FORMULATION AND EVALUATION OF DULOXETINE HYDROCHLORIDE DELAYED RELEASE CAPSULES

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

Register no: 26111012

UNDER THE GUIDANCE OF

DR. Grace Rathnam, Mpharm., PhD. `
(Institutional Guide)

Mr. Raja.S, Mpharm.
(Industrial Guide)

DEPARTMENT OF PHARMACEUTICS

C.L.BAID METHA COLLEGE OF PHARMACY

(An ISO 9001-2000 certified institute)

THORAIPAKKAM, CHENNAI-600097

April-2013

Phone : 24960151, 24960425
E-mail : principal@clbaidmethacollege.com
Website : www.clbaidmethacollege.org

C.L. Baid Metha College of Pharmacy

An ISO 9001 - 2000 certified institution

Jyothi Nagar, Old Mahabalipuram Road
Thorapakkam, Chennai - 600 097.

Affiliated to The Tamilnadu Dr. M.G.R. Medical University, Chennai.
Approved by Pharmacy Council of India, New Delhi, and
All India Council for Technical Education. New Delhi.

THE CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND EVALUATION OF DULOXETINE HYDROCHLORIDE DELAYED RELASE CAPSULES"** submitted to **THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY, CHENNAI-32** for the award of degree of **Master of pharmacy in Pharmaceutics** is a bonafide research work done by **Register No: 26111012** under my Guidance in the Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Chennai-600 097 during the academic year 2012-2013.

Place: Chennai-97

Phone : 24960151, 24960425
E-mail : principal@clbaidmethacollege.com
Website : www.clbaidmethacollege.org

C.L. Baid Metha College of Pharmacy

An ISO 9001 - 2000 certified institution

Jyothi Nagar, Old Mahabalipuram Road
Thorapakkam, Chennai - 600 097.

Affiliated to The Tamilnadu Dr. M.G.R. Medical University, Chennai.
Approved by Pharmacy Council of India, New Delhi, and
All India Council for Technical Education. New Delhi.

Prof. Dr. Grace Rathnam, M.pharm., PhD.,

Principal.

THE CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND EVALUATION OF DULOXETINE HYDROCHLORIDE DELAYED RELASE CAPSULES"** submitted to **THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY, CHENNAI-32** for the award of degree of **Master of Pharmacy in Pharmaceutics** is a bonafide research work done by **Register No:26111012** under the guidance of **DR. Grace Rathnam, Mpharm., PhD., Principal & HOD,** Department of Pharmaceutics, C. L. Baid Metha college of Pharmacy, Chennai-600 097 during the academic year 2012-2013.

Place: Chennai -97

Date:

Prof. Dr. GRACE RATHNAM, M. Pharm., Ph.D.,
Principal & HOD,
Department of Pharmaceutics,
C.L.Baid Metha college of Pharmacy,
Chennai-97.

DECLARATION

I hereby declare that the thesis entitled **"FORMULATION AND EVALUATION OF CAPECITABINE IMMEDIATE RELEASE TABLETS"** has been originally carried out by me under the supervision and guidance of **Mr. Raja.S.,** (Industrial guide) and **DR. Grace Rathnam, Mpharm., PhD,** (Institutional Guide) principal & HOD, Department of Pharmaceutics, C.L. Baid Metha college of Pharmacy,Chennai-97, during the academic year 2012-2013

Place: Chennai-97 **26111012**

Date: **Department of Pharmaceutics,**

C.L.Baid Metha college of Pharmacy,

Chennai-97.

ACKNOWLEDGEMENT

It is a great time for me to acknowledge those without whom, this work would not have been fruitful.

It gives me an immense pleasure in expressing my deep sense of gratitude to my respected guide **DR. Grace Rathnam, Mpharm., PhD., Principal & HOD,** C.L. Baid Metha college of pharmacy for his remarkable guidance, constant encouragement and every scientific and personal concern throughout the course of investigation and successful completion of this work.

I would like to express my immense gratitude to my industrial guide **Mr.Raja .S., M.Pharm., Head-R&D, Orchid PHARMA LTD,**IRUNGATUKOTTAI,CHENNAI**,** for providing the great opportunity to carry out the project in **ORCHID PHARMA LTD**, for his valuable guidance and support in each and every aspect of the project.

It is great pleasure and honor for me to owe gratitude to **Dr. Grace Rathnam M.Pharm, Ph.D**. principal for all her support and for giving a valuable guidance and scientific support to carry out this work.

I feel proud to express my hearty gratitude and appreciation to all my Teaching and Non-teaching Staff members of **C.L.Baid Metha College of Pharmacy** who encouraged to complete this work.

I feel proud to express my hearty gratitude to all my classmates. Also I want to thank all of those, whom I may not be able to name individually, for helping me directly or indirectly.

Last but not the least I wish to express my deepest sense to respect and love to my parents, for their constant support and encouragement throughout.

26111012

LIST OF TABLES

LIST OF FIGURES

Discussion

Summary and Conclusion

Bibliography

Dedicated

To my

Beloved Family

&

My friends

INTRODUCTION[1]

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided in to number of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm. Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet. The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulations and yet devoid of the danger of alteration in drug release profile and formulation behavior due to unit to unit variation, change in gastro-luminal pH and enzyme population[1]

ADVANTAGES OF MULTIPARTICULATE DRUG DELIVERY SYSTEMS[1,2]

- Increased bioavailability
- Reduced risk of systemic toxicity
- Reduced risk of local irritation
- Less gastric emptying time
- Less inter & intra subject variability
- Uniform drug absorption
- It provides uniform functional coating

Multiparticulates are discrete particles that make up a multiple unit system. They provide many advantages over single-unit systems because of their small size. Multiparticulates are less dependent on gastric emptying, resulting in less inter and intra-subject variability in gastrointestinal transit time. They are also better

distributed and less likely to cause local irritation. Much emphasis is being laid on the development of multiparticulate dosage forms in preference to single unit systems because of their potential benefits such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying.

There are many reasons for formulating a drug as a multiparticulate system for example, to facilitate disintegration in the stomach, or to provide a convenient, fast disintegrating tablet that dissolves in water before swallowing which can aid compliance in older patients and children After disintegration which occurs within a few minutes often even within seconds, the individual subunit particles pass rapidly through the GI tract. If these subunits have diameters of less than 2mm, they are able to leave the stomach continuously, even if the pylorus is closed. These results in lower intra and inter individual variability in plasma levels and bioavailability.

Drug safety may also be increased by using multiparticulate dosage forms, particularly for modified release systems. For example, if the film coat of a single-unit enteric coated tablet is damaged, the complete dose will be released into the stomach where it may cause pain or ulceration or reduced efficacy, depending on the reason for choosing the protection of the enteric coating. Equally, if there is damage to the film coating of a monolithic tablet with a sustained release formulation, this can lead to “dose dumping” and result in dramatic side effects. By contrast, in multiparticulate formulation, the release characteristics are incorporated into every single subunit and any damage only affects the release behaviour of the subunit involved, which represents a small part of the total dose, reducing the likelihood of safety problems.

Multiparticulates have a much lower risk of dose dumping than tablets single doses that are released accidentally (e.g., by fat) may cause higher incidence of adverse events, compared with multiple units,Because they are small and easy to swallow, multiparticulates are particularly suited to geriatric formulations &paediatric formulations. If a patient breaks a tablet in half so that he or she can

swallow it more easily, the tablet's coating layer often is compromised and it can no longer provide controlled drug release. Multiparticulates avoid this difficulty because they are small enough for geriatric patients to swallow them easily.

Dividing a dose into many multiparticulates helps distribute the drug slowly, evenly, and consistently. At any given time, multiparticulates are present in the stomach, the intestine, and other sites in the GI tract, which helps maximize drug absorption. Because multiparticulatesprovide smooth transit through the GI tract and are less dependent on gastric emptying, they greatly reduce the variability between patients' plasma profiles.

Multiparticulates size limits the exposure of the drug to the epithelium and reduces the possibility of irritating the GI tract and the bowel.

Multiparticulates can be used to improve convenience and patient compliance, too. For example, a manufacturer might choose to develop a formulation as a traditional tablet because it would allow the company to reach the patient relatively quickly. Afterward, the manufacturer could develop a multiparticulate dosage form of the same drug to provide modified release for increased bioavailability or once-daily application

In addition, multiparticulates can allow drug makers to provide patients with individualized dosing. For example, a company could package the pellets in a device that patients press to dispense individualized doses. A patient thus could take the appropriate dose for his or her weight or age group. And a dosage form that included instant- and extended-release multiparticulates could improve compliance by reducing the number of doses the patient must take each day

A generally accepted view is that multiparticulate systems perform better *in vivo* than single unit systems, as they spread out throughout the length of the intestine causing less irritation

Since multiparticulates enable good control of drug release, the dosage form is becoming more popular for drugs that treat chronic conditions. For these

reasons, cardiovascular drugs and blood-pressure medicines could benefit from multiparticulates.

DISADVANTAGES

- Low drug loading
- Proportionally higher need for excipients
- Lack of manufacturing reproducibility and efficacy
- Large number of process variables
- Multiple formulation steps
- Higher cost of production
- Need of advanced technology
- Trained/skilled personal needed for manufacturing

Multiparticulates are discrete particles that make up a multiple unit system. They provide many advantages over single-unit systems because of their small size. Multiparticulates are less dependent on gastric emptying, resulting in less inter and intra-subject variability in gastrointestinal transit time. They are also better distributed and less likely to cause local irritation[3.]

Much emphasis is being laid on the development of multiparticulate dosage forms in preference to single unit systems because of their potential benefits such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying.

There are many reasons for formulating a drug as a multiparticulate system for example, to facilitate disintegration in the stomach, or to provide a convenient, fast disintegrating tablet that dissolves in water before swallowing which can aid compliance in older patients and children After disintegration which occurs within a few minutes often even within seconds, the individual subunit particles pass rapidly through the GI tract. If these subunits have diameters of less than 2 mm, they are able to leave the stomach continuously, even if the pylorus is

closed. These results in lower intra and inter individual variability in plasma levels and bioavailability.

Drug safety may also be increased by using multiparticulate dosage forms, particularly for modified release systems. For example, if the film coat of a single-unit enteric coated tablet is damaged, the complete dose will be released into the stomach where it may cause pain or ulceration or reduced efficacy, depending on the reason for choosing the protection of the enteric coating. Equally, if there is damage to the film coating of a monolithic tablet with a sustained release formulation, this can lead to “dose dumping” and result in dramatic side effects. By contrast, in multiparticulate formulation, the release characteristics are incorporated into every single subunit and any damage only affects the release behaviour of the subunit involved, which represents a small part of the total dose, reducing the likelihood of safety problems.

Multiparticulates have a much lower risk of dose dumping than tablets single doses that are released accidentally (e.g., by fat) may cause higher incidence of adverse events, compared with multiple units,Because they are small and easy to swallow, multiparticulates are particularly suited to geriatric formulations &paediatric formulations. If a patient breaks a tablet in half so that he or she can swallow it more easily, the tablet's coating layer often is compromised and it can no longer provide controlled drug release. Multiparticulates avoid this difficulty because they are small enough for geriatric patients to swallow them easily.

Dividing a dose into many multiparticulates helps distribute the drug slowly, evenly, and consistently. At any given time, multiparticulates are present in the stomach, the intestine, and other sites in the GI tract, which helps maximize drug absorption. Because multiparticulates provide smooth transit through the GI tract and are less dependent on gastric emptying, they greatly reduce the variability between patients' plasma profiles.

Multiparticulates size limits the exposure of the drug to the epithelium and reduces the possibility of irritating the GI tract and the bowel.

Multiparticulates can be used to improve convenience and patient compliance, too. For example, a manufacturer might choose to develop a formulation as a traditional tablet because it would allow the company to reach the patient relatively quickly. Afterward, the manufacturer could develop a multiparticulate dosage form of the same drug to provide modified release for increased bioavailability or once-daily application

In addition, multiparticulates can allow drug makers to provide patients with individualized dosing. For example, a company could package the pellets in a device that patients press to dispense individualized doses. A patient thus could take the appropriate dose for his or her weight or age group. And a dosage form that included instant- and extended-release multiparticulates could improve compliance by reducing the number of doses the patient must take each day

A generally accepted view is that multiparticulate systems perform better *in vivo* than single unit systems, as they spread throughout the length of the intestine causing less irritation. Since multiparticulates enable good control of drug release, the dosage form is becoming more popular for drugs that treat chronic conditions. For these reasons, cardiovascular drugs and blood-pressure medicines could benefit from multiparticulates.

MECHANISM OF DRUG RELEASE FROM MULTI-PARTICULATES[1]

The mechanism of drug release from multiparticulates can be occur in the following ways:

Diffusion

On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion

Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

Osmosis

In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating

MAKING MULTIPARTICULATES

Fluid-bed processor

The simplest manufacturing technique is to layer the liquid drug onto inert spherical particles made of sugar or microcrystalline cellulose this process is done using a bottom spray with a Wurster column attachment on a fluid-bed processor.

Extrusion and Spheronization

Another common manufacturing method relies on extrusion and spheronization. First, operators force a blended, wet mass of drug and excipients through aporous plate with an extruder. Then the fragments are loaded onto a revolving disk with a chosen surface roughness, and the disk's rotation forms rounded pellets.

Spray Congealing

In hot-melt spray congealing, scientists melt a waxy polymer and mix an API into it, The API must be thermally stable enough to withstand the polymer's melting temperatures of 60–70 °C. Droplets of this molten mixture fall onto a fast-rotating disc and are dispersed into fine particles that solidify as they travel, within several centimeters. These fine particles become spherical multiparticulates that can be encapsulated and used for modified release.

Centrifugal coating granulator

It is based on layering the drug directly in powdery form where drug loading occurs by gravity and adhesion is ensured by a liquid binder sprayed onto the cores. The layering process is particularly suitable for production of small drug loaded units, multiples of which are placed into capsules for patient delivery.

DESIGN OF MULTIPARTICULATE DRUG DELIVERY SYSTEMS[1]

Intestinal Protective Drug Absorption System

Intestinal protective drug absorption system (IPDAS) (Figure1) is a multiparticulate tablet technology that hasbeen developed to enhance the gastric tolerability of potentially irritant or ulcerogenic drugs such as the NSAIDs.

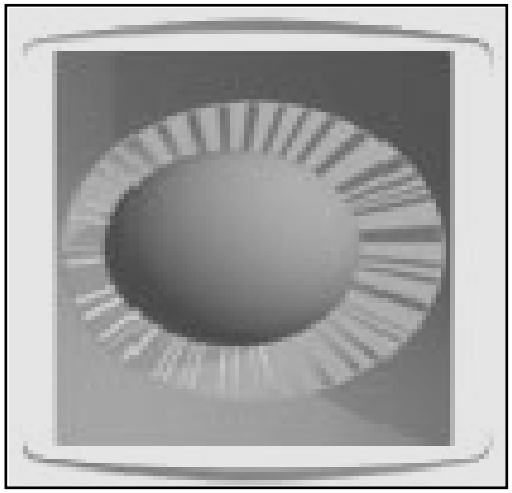


Fig 1: Intestinal Protective Drug Absorption System

It consists of high density controlled release beads that are compressed into a tablet form. The beads may be manufactured by techniques such as extrusion spheronization and controlled release can be achieved with the use of different polymer systems to coat the resultant beads. Alternatively, the drug can also be coated into on an inert carrier such as non-pareil seeds to produce instant release

multiparticulates. Controlled release can be achieved by the formation of a polymeric membrane on to these instant release multparticulates.

Once an IPDAS tablet is ingested; it rapidly disintegrates and disperses beads containing the drug in the stomach which subsequently pass into the duodenum and along the gastrointestinal tract in a controlled and gradual manner, independent of the feeding state. Release of active ingredient from the multiparticulates occurs through a process of diffusion either through the polymeric membrane and /or the micro matrix of the polymer/active ingredient formed in the extruded/spheronizedmultiparticulates. The intestinal protection of IPDAS is by virtue of the multiparticulate nature of the formulation which ensures wide dispersion of irritant drug throughout the gastrointestinal tract[4].

Spheroidal oral drug absorption systems

Spheroidal Oral Drug Absorption System (SODAS) (Figure 2) is a multiparticulate technology that enables the production of customized dosage forms and responds directly to individual drug candidate needs. It can provide a number of tailored drugs release profiles including immediate release of drug followed by sustained release to give rise to a fast onset of action which is maintained for 24 hours. Alternatively, the opposite scenario can be achieved where drug release is delayed for a number of hours[5].

Fig 2: Spheroidal Oral DrugAbsorption System

Programmable Oral Drug Absorption System

Programmable Oral Drug Absorption System (PRODAS) (Figure 3) is presented as a number of mini tablets contained in hard gelatin capsule. It thus combines the benefits of tableting technology within a capsule. It is possible to incorporate many different minitablets, each one formulated individually and programmed to release drug at different sites within the GIT. These combinations may include immediate release, delayed release, and/or controlled release mini tablets. It is also possible to incorporate mini tablets of different sizes so that high drug loading is possible. Their size ranges usually from 1.5 – 4 mm in diameter[6].

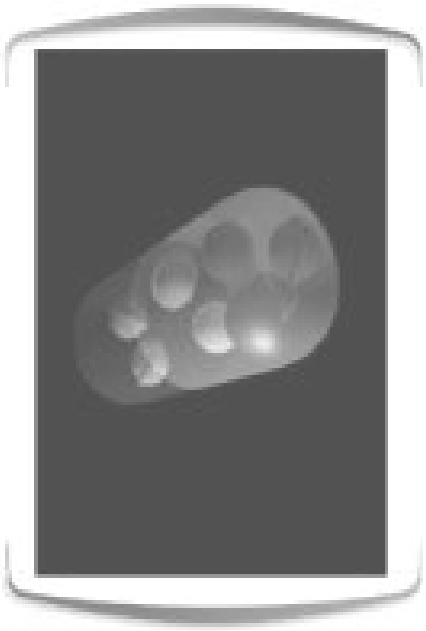


Fig 3: Programmable Oral Drug Absorption System

Diffucaps[7]:

In this multiparticulate system, drug profiles are created by layering an active drug onto a neutral core such as sugar spheres, crystals or granules followed by the application of a rate-controlling, functional membrane (Figure 4). The coating materials can be water soluble, pH dependent or independent or water insoluble depending on the individual needs of compound. The resultant beads are small in

size approximately 1mm or less in diameter. By incorporating beads of differing drug release profiles into hard gelatin capsules, combination release profiles can be achieved. It is possible to customize any combination of sustained release, pulsatile release and immediate release profiles depending on the specific needs of the product. The drug layering process can be conduct either from aqueous or solvent based drug solutions.

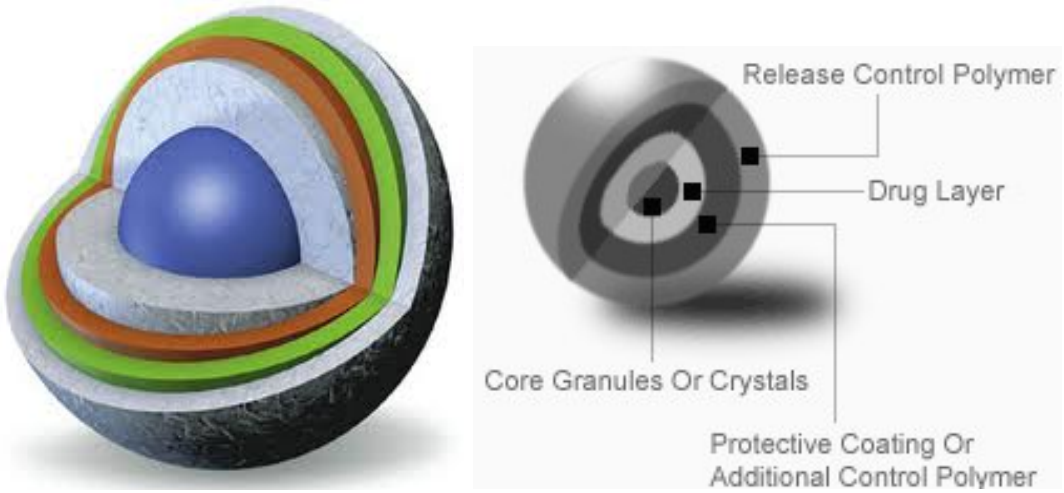


Fig 4: Diffucaps

Diffucaps beads are small in size, approximately 1mm in diameter, and are filled into a capsule to create the final dosage form. Beads of differing drug release profiles can be easily combined in a single capsule providing high levels of control over release profiles. Diffucaps beads of different drugs can be combined to make convenient single dose units for combination therapies.

Diffucaps consist of different layers, The number of layers and its nature depend on the nature of formulation and nature of drug. a typical diffucaps consist of a core material spherical in shape called non peril seeds .A core material of uniform size and of spherical in shape is needed to do uniform coating. Over the core the drug is layered with uniform thickness. The drug layer is further covered by a barrier which prevent the direct interaction of drug with polymer used for modified release. The functional coating is done over the barrier coated pellets to get the desired

modified release pattern. Over the function coating an optional top coating is done to get the moisture protection, & lubrication.

Mini-Tablets

The MINITABS technology (Figure 5) is unique in that it offers the advantages of a tablet combined with those of a multiparticulate drug form they are tiny (2mm x 2mm) tablets containing gelforming excipients that control drug release rate. Additional membranes may be added to further control releaserate. The small size of minitabs means that they can be filled into capsules as a final dosage form. As a result, combination products can be developed to allow for two or more release profiles within a single capsule. Minitabs offer high drug loading, the ability to fine tune release rates for targeted delivery andcontent uniformity for more accurate dosing. Minitabs offer high drug loading, a wide range of release rate designs, and fine tuning of these release rates. The capsules can be opened and the contents used as a "sprinkle" formulation[8].

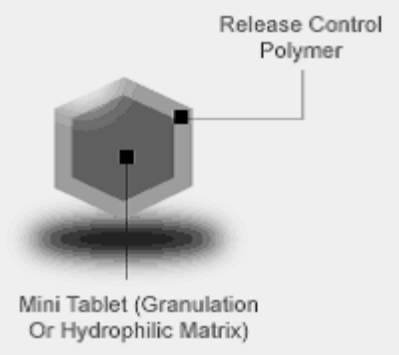


Fig 5:Minitabs

It is a widely acceptable statement that solid oral dosage forms, mainly tablets are most acceptable form for delivering medication. There are some new variations emerging such as mini-tablets, offering formulation flexibility. Mini-tablets are small tablets with diameter equal to or less than3mm that are filled in capsule, or at times compressed into tablets. It is possible to incorporate many different mini-tablets each designed to release drug at different sites within the GIT.

The combinations may include IR, DR and/or CR . It is possible to incorporate different drugs in mini-tablets used for concurrent disease or combination of drugs to improve therapeutic outcome, while delivering release rates of each accordingto disease needs. It can also offer a good solution for various problems faced currently in pharmaceutical industry representing a lack of dosage forms which are suitable for pediatrics.

Mini-tablets combine the established tableting technology with the multiparticulate dosage forms. Additional benefits are regular shape, excellent size uniformity, and smooth surface therebyoffering best substrate for coating with different polymer materials. Mini-tablets can be produced by DC or wet or dry granulation and can be manufactured by normal tableting machines with only minorequipment modifications. For example, to increase the production speeds, multiple tip tooling has beenemployed routinely. It can also be coated using perforated coating pan or a fluid bed apparatus[9]

Fig 6: Mini-tablets with die, upper and lower punch[10].

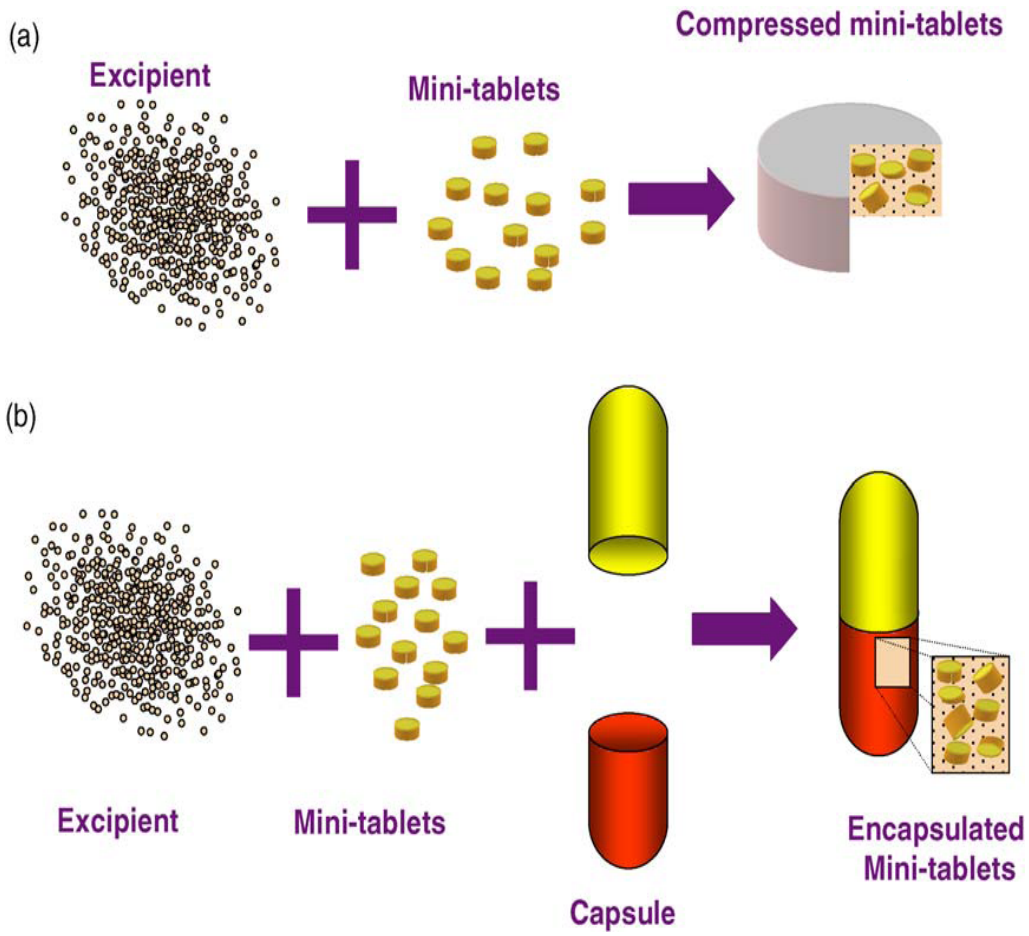


Fig 7: Mini-tablets delivered (a) as a tablet or a (b) capsule[11]

Mini-tablet is a good substitute for pellets because they can be easily manufactured and are also favors coating in order to produce sustain drug release. Further, dosage forms containing mini-tablets are smaller when compared to granules and pellets. Hence, developing mini-tablets for controlled drug release for oral route is the important focus in the research field. Likewise, matrix mini-tablet has also been developed.

Several mini-tablets can be placed in a capsule; hence tablets with different content, dose and release characteristics can be included. Inclusion of IRMT permits the development of rapid acting EMT dosage forms with optimal pharmacokinetic profiles for rapid action. In EMT various sustained drug release profiles can be designed by combining different quantities of mini-tablets, and can also include combination of different drugs, thereby improving patient compliance.

To bring about immediate release, IRMT contained low substituted HPC as a disintegrant, and were prepared by simply coating mini-tablets with HPMC.

The SRMT is coated with a mixture of EC and HPMC. Mixtures of polymers were used for controlled release drug delivery system to allow pore-mediated diffusion through the film.[12]

The advantages of SRMT over single unit dosage forms are

- Less risk of dose dumping
- Less intra and inter subject variability
- Child acceptability
- Dosing flexibility
- Taste masking
- High degree of dispersion in GIT thus minimizing the risk of high local drug concentrations[13]
- Excipient tolerability for drug substance with bitter taste or potential chemical instability in liquid[10]

Advantages

- Mini-tablets pack large quantity of API in a form that can be easily swallowed.
- Due to its small size, it can quickly and uniformly pass through the stomach, and is also independent of meals
- Good alternative to pellets and easier to manufacture
- Manufacturing different doses in one tablet forming step and filled into capsule according to dose
- This brings up the opportunity to combine tablets with different coating in one capsule[14]

- ❖ It's an easy way to produce complex release profiles, i.e. initial and maintenance dose in one capsule lowers the risk of dose dumping
- ❖ Several chemically incompatible drugs pressed into mini-tablets, coated and combined in one capsule.
- ❖ Mini-tablets also offers an alternative for pellets because of their ease of manufacture, because of dosage forms of equal dimension and weight with smooth regular surface are produced in a reproducible and continuous way[13]

Stabilized Pellet Delivery System:

Stabilized pellet delivery system technology uses functional polymers or a combination of functional polymers and specific additives, such as composite polymeric materials to deliver a drug to a site of optimal absorption along the intestinal tract. The active drug is incorporated in multiparticulate dosage forms such as DIFFUCAPS or Eurand MINITABS, which are then subsequently coated with pH dependent/independent polymeric membranes that will deliver the drug to the desired site. These are then filled into hard gelatin capsules. This technology is designed specifically for unstable drugs and incorporates a pellet core of drug and protective polymer outer layer(s)[1]

Pelletized Delivery System:

Pelletized Delivery System (PDS) is a sustained release system using pellets or beads manufactured using arumerization/ pheronization/ pelletization techniques or by layering powders or solutions on nonpareil seeds. Release modulating polymers are sprayed on the beads using various coating techniques. The coated beads are filled in to hard gelatin capsules. Drug release occurs by diffusion associated with bioerosion or by osmosis via the surface membrane. The release mechanism can be pH-activated or pH-independent. The beads can be formulated to produce first order or zero order release.[1]

Pelletised tablet:

Pelletised tablet (Peltab®) system utilizes polymer-coated drug pellets or drug crystals,which are compressed into tablets. In order to provide a controlled release, a water insoluble polymer is used to coat discrete drug pelletsor crystals, which then can resist the action of fluids in the GIT. This technology incorporates a strong polymer coating enabling the coated pellets to be compressed into tablets without significant breakage[1].

Multiparticle Drug Dispersing Shuttle:

Multiparticle drug dispersing shuttle (Multipart®) consists of a tablet carrier for the delivery of controlled release beads or pellets through the GIT which preserves the integrity and release properties of the beads. The distribution of the beads is triggered by the disintegration of the tablet carrier in the stomach. Drug release from the beads is triggered by super disintegration of the tablets. It can be pH-activated or pH-independent and can occur by disintegration or osmosis. The beads can be formulated to produce first or zero order release[1].

Macrocap®:

Macrocap® consists of immediate release beads made by extrusion/ spheronization/ pelletization techniques or by layering powders or solutions on nonpareil seeds. Release modulating polymers are sprayed on the beads using various coating techniques. The coated beads are filled in hard gelatin capsules. Drug release occurs by diffusion associated with bioerosion or by osmosis via the surface membrane. The release mechanism can be pH-activated or pH independent. The beads can be formulated to produce first or zero order release[1].

Orbexa®:

Orbexa® technology is a multiparticulate system that enables high drug loading and is suitable for products that require granulation. This technology

produces beads that are of controlled size and density using granulation, extrusion and spheronization techniques. This process is unique in that it allows for higher drug loading than other systems, is flexible and is suitable for use with sensitive materials such as enzymes[1].

KV/24:

KV/24 is a patented, multiparticulate drug delivery technology that encapsulates one or more drug compounds to achieve release in a pre-determined fashion over a 24-hour period after oral administration. KV/24 technology is based upon coating a neutral core (nonpareiled bead) with a drug substance, then sequentially coating with one or more polymers to achieve a once-a day release profile. The drug can either be combined with the neutral core or incorporated into the coating process[1].

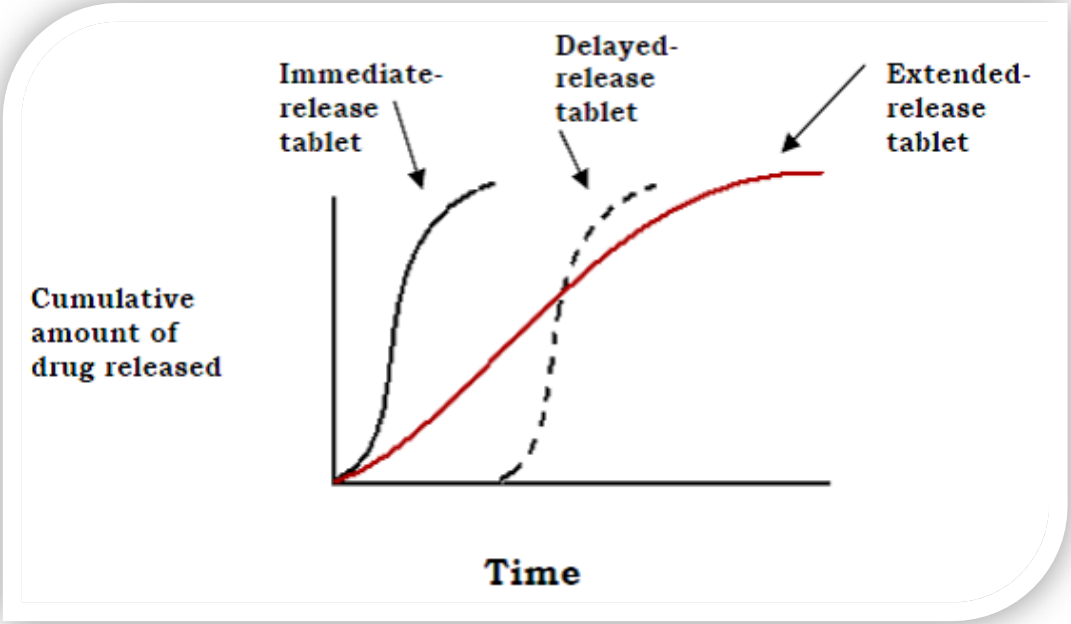
Flashtab:

Flashtab technology is a fast dissolving/disintegrating oral tablet formulation. It is a combination of taste masked multiparticulate active drug substances with specific excipients compressed into tablets. A disintegrating agent and a swelling agent are used in combination with coated drug particles in this formulation to produce a tablet that disintegrates in the mouth in less than one minute. These oro-dispersible tablets disperse rapidly before the patient swallow them[1].

DELAYED RELEASE FORMULATION

The United States Pharmacopeia (USP) defines *delayed-release tablets* as enteric-coated to delay release of the medication until the tablet has passed through the stomach to prevent the drug from being destroyed or inactivated by gastric juices or where it may irritate the gastric mucosa[15].

Figure 8: Comparative dissolution profile of an immediate release and modified release formulations



Delayed release dosage forms redesigned to release the drugs at a time rather rapidly after administration the delay may be time based or based on influence of physiological conditions like G.i.t pH.

Drugs contained in such a system are those that are

1. Destroyed in the stomach
2. Destroyed by the intestinal enzymes
3. Known to cause gastric distress
4. Absorbed from specific intestinal site
5. Meant to exert local effect at a specific gastrointestinal site

Types of delayed release systems

1. Intestinal release systems
2. Colonic release systems

INTESTINAL RELEASE SYSTEMS

A drug may be enteric coated for intestinal release to prevent destabilization in gastric pH or to release the drug in intestinal pH[16].

COLONIC RELEASE SYSTEMS

Drugs are poorly absorbed through colonmay be delivered to such a site for 2 reasons

1. Local action in the treatment of ulcerative colitis
2. Systemic absorption of protein and peptide drugs

Advantage is taken of the fact that pH sensitive bio-erodible polymers like polymethacrylates release the medicaments only at the alkaline pH of the colon or use of divinyl benzene cross linked polymers that can be cleaved only by the azoreductase of the colonic bacteria to release the free drug for local effect or systemic absorption. The most commonly used pharmaceutical delayed releaser solid oral dosage forms include capsules, tablets, granules and pellets[17]

Enteric coating18

An **enteric coating** is a barrier applied to oral medication that controls the location in the digestive system where it is absorbed. *Enteric* refers to the small intestine; therefore enteric coatings prevent release of medication before it reaches the small intestine.

Most enteric coatings work by presenting a surface that is stable at the highly acidic pH found in the stomach, but breaks down rapidly at a less acidic (relatively more basic) pH. For example, they will not dissolve in the acidic juices of the stomach (pH ~3), but they will in the higher pH (above pH 5.5) environment present in the small intestine. Materials used for enteric coatings include fatty acids, waxes, shellac and plastics, plant fibers.

Advantages of enteric coating[19,20]:

- To protect drugs that are unstable in acid from disintegrating in thegastric juices (e.g., antibiotics, enzymes, peptides, proton pump inhibitors)
- To protect the stomach from aggressive drugs that irritate the gastricmucosa (e.g., acetylsalicylic acid, iron compounds)
- pH-dependent controlled release of drugs for optimal absorption
- Delayed release
- GI targeting of different sections of the small intestine or of the colon(absorption window, targeting localized effects
- Colon targeting for local treatment and systemic therapies

Solid dosage forms containing drugs that are susceptible to degradation in the stomach due to the acidic environment or gastric enzymes have been stabilized with an enteric film coating. Enteric coating has traditionally been used to prevent drug release in the upper GI tract. A decrease in gastric irritation caused by drugs, such as aspirin, can also be achieved by enterically coating the solid dosage form.In addition, enteric coatings can be used to target drug release in the small intestine.

Ideal characteristics of enteric coating polymers

1. Resistance to gastric fluids
2. Ready susceptibility or permeability to intestinal fluids
3. Compatibility with most coating solution components and the drug substrates
4. Non toxicity
5. Formation of continuous film
6. The film should not change on aging

7. Low cost
8. Ease of application

ENTERIC POLYMERS USED FOR FILM COATING OF SOLID DOSAGE FORMS[21]

Enteric polymers currently used to coat pharmaceutical dosage forms include cellulose, vinyl, and acrylic derivatives. These polymers exhibit resistance to gastric fluids yet are readily soluble or permeable in intestinal fluid. Enteric polymeric materials are primarily weak acids containing acidic functional groups, which are capable of ionization at elevated pH. In the low pH of the stomach, the enteric polymers are unionized, and therefore, insoluble. As the pH increases in the intestinal tract, these functional groups ionize, and the polymer becomes soluble in the intestinal fluids. Thus, an enteric polymeric film coating allows the coated solid to pass intact through the stomach to the small intestine, where the drug is then released for absorption through the intestinal mucosa into the human body where it can exert its pharmacologic effects.

Cellulose acetate phthalate (CAP)

The CAP polymer exhibits rapid dissolution at a pH greater than 6 and is relatively permeable to moisture and gastric juices. Due to its high moisture permeability, CAP is susceptible to hydrolytic decomposition. Phthalic and acetic acid molecules may hydrolyze during storage and significantly compromise the degree of enteric protection that the film coating provides. The addition of a plasticizing agent has been shown to improve the water resistance of CAP films

Polyvinyl acetate phthalate (PVAP)

PVAP is another enteric polymer commonly used to coat solid dosage forms .This polymer is structurally similar to CAP containing the dicarboxylicpthalic acid in a partially esterified form. Faster release of drug

components occurs with PVAP because dissolution of this polymer occurs at a pH of approximately 5.0. Due to its lower moisture permeability.

Hydroxypropyl methylcellulose phthalate (HPMCP)

Esterified HPMC with pthalic anhydride to produce hydroxypropyl methylcellulose phthalate (HPMCP), which rapidly dissolves in the upper intestinal tract. Due to the limited compatibility of HPMCP with several types of plasticizers, hydroxypropyl methylcellulose acetate succinate (HPMCAS) was developed. The presence of ionizable carboxyl groups in the HPMCAS structure cause the polymer to solubilize at high pH (> 5.5 for the LF grade and > 6.8 for the HF grade). This polymer exhibits good compatibility with a variety of plasticizing agents

Methacrylic acid copolymers

Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethylmethacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. These polymers are produced by an emulsion polymerization process and are commercially available in several forms. The dissolution properties of these polymers are dependent on the content of carboxyl groups in the polymer. These acrylic derivatives are commercially available from Eudragit®. Eudragit L 30 D-55 is an aqueous-based dispersion containing USP/NF methacrylic acid copolymer Type C and exhibits dissolution above pH 5.5. Acryl-Eze® is a relatively new fully formulated acrylic enteric coating system based on spray-dried USP/NF methacrylic acid copolymer Type C, containing plasticizer(s), pigment(s), and neutralizing agents in a powder form for redispersion in water. Eudragit FS 30 D is an aqueous-based acrylic polymeric dispersion consisting of methacrylic acid, methyl acrylate, and methyl methacrylate. This polymer contains fewer carboxyl groups and thus dissolves at a higher pH (> 6.5).

Most commonly used pH-dependent coating polymers for peroral delivery are methacrylic acid copolymers, Eudragit L100 and Eudragit S100, which dissolve at pH 6.0 and 7.0 respectively. The combination of these two polymers in various ratiosmakes it possible to manipulate drug release within 6.0-7.0 pH range.

Table No.1 Enteric polymers utilized in development of modified-release formulations

S.NO	Enteric polymers	Optimum pH For Dissolution
1	Polyvinyl acetate phthalate (PVAP)	5
2	Cellulose acetate trimellitate (CAT)	5.5
3	Hydroxypropyl methylcellulose phthalate (HPMCP)	>5.0
	A) HP-50	>5.5
	B) HP-55 and HP-55S	
4	Hydroxypropylmethylcellulose acetate succinate (HPMCAS)	>5.5
	A) LF Grade	>6.0
	B) MF Grade	
	C) HF Grade	>6.8
5	Methacrylic acid copolymer, Type C (Eudragit® L100-55) Methacrylic acid copolymer dispersion (Eudragit® L30D-55)	> 5.5
6	Methacrylic acid copolymer, Type A (Eudragit L-100 and Eudragit® L12,5)	> 6.0
7	Cellulose acetate phthalate (CAP) (Aquateric®)	6
8	Methacrylic acid copolymer, Type B (EudragitS-100 and Eudragit® S12,5)	>7.0
9	Eudragit® FS30D	> 7.0
10	Shellac (MarCoat 125 and 125N)	7
11	Acryleze MP	7
12	NS Enteric Surelase	7.3

LITERATURE REVIEW

NS Dey, S Majumdar and MEB Rao et al., (2008)[1] reviewed on multiparticulate drug delivery systems. They are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The release of drug from microparticles depends on a variety of factorsincluding the carrier used to form the multiparticles and the amount of drug contained in them. Consequently,multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development

Lailafathima Ali sagar et al., (2006)[20] studied the in vivo behaviour of pellets and reported that the mean gastric emptying time for pellets was very less than tablet. And the mean transit through the small intestine did not vary significantly for both the formulations. And pellets were having longer residence time in large intestine than tablets

PareshPrajapati A et al., (2010)[22] prepared ocular mini tablets of ocular mini tablets by single punch compression machine equipped with 4mm flat round tooling specially developed in the lab. Invivo release of drug from ocular mini tablets was determined at different dissolution volume and rotational speeds. 3 in vitro methods were used for the determination of drugs and their release of drugs from various ophthalmic preparations was determined in rabbit eye and invitro release rate of the drug was determined at different rotational speed. 3 in vitro methods were used for the determination of the drugs and their release from various ophthalmic preparations by using static method stirred (paddle) method and rotating vial method finding correlation coefficient and plotting a scattered diagram established in vitro= in vivo relationship by rotating vial method matched with the invivo results. Specific hydrodynamic and volume showed high in vitro –in vivo correlation

Carla M. Lopes, Jose Manuel Sousa Lobo et al., (2006)[11] Compressed mini-tablets systems as a biphasic delivery system designed for zero-order sustained drug release. The outer layer thatfills the void spaces between the mini-tablets were formulated to release the drug in a very short time (fast release), while the mini-tablets provideda prolonged release. Different composition (HPMC or EC) and number (10 or 21) of mini-tablets were used to obtain different drug release rates.The in vitro performance of these systems showed the desired biphasic behaviour: the drug contained in the fast releasing phase (powder enrobingthe mini-tablets) dissolved within the first 2 min, whereas the drug contained in the mini-tablets was released at different rates, depending uponformulation. Based on the release kinetic parameters calculated, it can be concluded that mini-tablets containing HPMC were particularly suitableapproaching to zero-order (constant) release over 8 h time periods.

Domenico De Berardis et al., (2007)[23] has reviewed to elucidate current facts and views about the role of Duloxetine in the treatment of ADs. In February 2007, duloxetine was approved by FDA for the treatment of generalized anxiety disorder (GAD). The results of trials evaluating the use of duloxetine in the treatment of GAD was supportive on its efficacy even if further studies on long-term use were needed. Apart from some interesting case reports, no large studies were, to date, present in literature about duloxetine and other ADs such as panic disorder, social anxiety disorder, obsessive-compulsive disorder and post-traumatic stress disorder. Therefore, the clinical efficacy and the relative good tolerability of duloxetine may be further investigated to widen the therapeutic spectrum of ADs.

Timothy Smith et al., (2007)[24] did a review article to discuss the background of painful diabetic neuropathy, the pharmacology of Duloxetine, and its safety and efficacy in clinical trials and long-term observations. The authors also commented on its use in clinical practice. Results from controlled clinical trials reveal that Duloxetine administered at 60 mg *q.d* or 60 mg *b.i.d* was efficacious in treating diabetic neuropathic pain relative to placebo. Positive treatment outcomes were also seen for other measures of pain and quality of life. A minor but statistically significant increase in blood glucose compared with placebo treated

patients has been observed in controlled clinical trials. Otherwise, controlled and open-label clinical studies have demonstrated a high degree of safety and tolerability for the compound. These findings provide support for the proposed role of serotonin and nor epinephrine as key mediators of the descending pain inhibition pathways of the brain stem and spinal cord

Melanie E. Hunziker et al., (2005)[25] reviewed the literature on Duloxetine with regard to itspharmacodynamics, pharmacokinetics, clinical efficacy, and tolerability. A comprehensive search of MEDLINE was performed using the terms Duloxetine, Cymbalta, and major depressive disorder, with norestriction on year. The Eli Lilly and Company clinical trial registry, and abstracts and posters from recentAmerican Psychiatric Association meetings were also reviewed. Duloxetine exhibits linear, dose dependent pharmacokinetics across the approved oral dosage range of 40 to 60 mg/day. No dose adjustment appears to be needed based on age. Duloxetine has shown efficacy in reducing depressive symptoms compared with placebo, and Duloxetine recipients have shown significant improvements in global functioning compared with placebo (both, $P < 0.05$). Response and remission rates have beencomparable to or greater than those seen with Fluoxetine or Paroxetine. Duloxetine was generally well tolerated, with nausea, dry mouth, and fatigue being the most common treatment-emergent adverse effects. Cardiovascular adverse effects do not appear to result in sustained blood pressure elevations, QTc-interval prolongation, or other electrocardiographic changes. Conclusions: Based on the availableevidence, Duloxetine was a well-tolerated and effective treatment for MDD in adults. Randomized head to-head comparisons against established antidepressants were needed to determine the relative safety and efficacy of Duloxetine.

Muhammad Rashedul Islam et al., (2010)[26] did an investigation to develop a delayed release pellet dosage form of Duloxetine hydrochloride. Drug loaded nuclei was prepared using powder-layering technique in a conventional coating pan. The nuclei was coated with an acid resistant acrylic polymer (Eudragit L30 D55) in a wurster coater to different thickness equivalent to theoretical polymer load 25%, 30%, 35% and 40% w/w on dry basis. The in-vitro dissolution studies

were conducted in 0.1N HCl (pH~1.1) for 2 hours followed by phosphate buffer (pH 6.8) for 1 hour with USP dissolution tester (Type II). Enteric coated pellets with polymer load 25% and 30% failed to provide require acid resistant to the pellets but very insignificant amount of drug was leached from the coated pellets in acid phase with polymer load 35% and 40% in the acidic phase, whereas almost the whole amount of drug was released in the buffer phase. The results generated in this study showed that proper selection of polymer materials based on their physiochemical properties as well as polymer load is important in designing delayed release pellets dosage form with acceptable dissolution profile

NelePoelvoorde et al., (2009)[27] developed themulti-particulate formulation of viable bacteria for oral and vaginal delivery usingEudragit® FS30D as enteric polymer & PVA-based coating (Opadry® II and Opadry® AMB) before enteric coating as a sub coat. The result concluded that subcoatings have been used successfully prevents direct contact between acid-labile drug and the acidic functional groups of the enteric coating. The Layered pellets were protected by Eudragit® FS30D against the gastric fluid, resulting in an acceptable cell load of 1.4 × 108 cfu/100 mg after gastric passage

V.M. Castano et al., (2008)[28] nanoencapsulation of Acetyl Salicylic Acid (ASA) was carried out by a modified double emulsion, using an enteric coating of the copolymers Eudragit L-100 and L-30-D-55 as polymeric matrix. The best results of the nanoencapsulation NPs process were reached with the combination of the copolymer Eudragit L-100 and L-30 D-55, showing nanoparticles yield and encapsulation efficiency higher than 90% and release profiles with smaller burst. The release profiles indicate that the matrix used was suitable to prevent the contact of the active principle with the gastric medium and that this device could achieve a more efficient release in the intestine.

Fude Cui et al., (2007)[29] formulated enteric-soluble solid-state emulsion to enhance the stability of oily drugs in the gastric fluid. The ESE was prepared by spreading liquid o/w-emulsions on a flat glass and drying at the oven maintained at 40^0C. Aerosil 200 was applied as solid carrier and emulsifier. Eudragit® L30D-55

was used as enteric coating material droplet size distribution of the primary emulsions and the emulsion after reconstitution of zedoary turmeric oil (ZTO) ESE in the phosphate buffer were also measured. When ZTO ESE was immersed into phosphate buffer (pH 6.8), the stable emulsion was formed in 20 min, but the release was obviously suppressed when it was exposed to the gastric fluid. It was concluded that preparation of enteric-soluble solid-state emulsion by the present method for oral oily drug was feasible.

Pao-Chu Wu et al., (2006)[30] studied the effect of eudragit and enteric polymer composite on the Release of nicardipine. In this study, the water-insoluble polymers such as eudragit RL (RL) and Eudragit RS (RS) were used as retardants to prepare the sustained release dosage form of nicardipine/polymer solid dispersion by solvent evaporation method. The enteric polymers such as hydroxypropyl methylcellulose acetate succinate, LF grade (HPMCAS) and hydroxypropyl methylcellulose phthalate, HP-55 grade (HPMCP) were incorporated into the drug/polymers solid dispersions to modify the release rate of drug. The effects of the sustained release of nicardipine from drug/ Eudragit/enteric polymer solid dispersions were evaluated by the dissolution it was found that the dissolution efficiencies of drug were increased 2.35-21.08 folds with the addition of 20-40%of enteric polymer in pH 6.8 media.

Su-Yun Lyu et al., (2004)[31] studied the effect of Enteric Coated Granules of Mistletoe Lectinresults indicated that Eudragit, produced outstanding results with ideal release profiles and only minimal losses of cytotoxicity after manufacturing step.

S.Bozdağ et al., (1999)[19] formulated enteric coated omeprazole tablets usingHPMCP Eudragit® S-100, CAP and the study revealed that HPMCP & CAP were excellent polymers for releasing the drug atintestinal pH with least release in stomach.

Shin Etsu Chemical et al., (2006)[32] Aqueous Dispersion coating using Shin Etsu AQOAT ® preparation of coating dispersion.

Patrick jansen et al., (1998)[33] characterised the formation of succinamide and phthalamide impurities on interaction of Duloxetine Hcl with enteric polymers such as HPMCAS & HPMCP respectively, and the rate of formation is high in accelerated stability conditions.

Gang Cheng et al., (2004)[34] conducted a study on Time- and pH-dependent colon-specific drug delivery for orally administered diclofenac sodium and 5-aminosalicylic acid DS tablets and 5-ASA pellets were coated by ethyl cellulose (EC) and methacrylic acid copolymers (Eudragit® L100 and S100), respectively. The in vitro release behaviour of the DS coated tablets and 5-ASA coated pellets were examined Release profile of time-dependent DS coated tablets was not influenced by pH of the dissolution medium, but the lag time of DS release was primarily controlled by the thickness of the coating layer. The thicker the coating layer, the longer the lag time of DS release is. 5-ASA release features from the coated pellets depended upon both the combination ratio of the Eudragit® L100 and S100 pH-sensitive copolymers in the coating formulation and the thickness of the coating layer.

Norihitoshimono et al., (2003)[35] a multiparticulate chitosan-dispersed system which was composed of the drug reservoir and the drug release-regulating layer was developed for drug delivery**.** Enteric-coated drug coreswere prepared to remain intact in the stomach by using Enteric components (EudragitL100-55) and then to releasethe active ingredient in the upper small intestine.

Sureteric ®[36] is a complete aqueous film coating formulation developed to meet the delayed release coating needs of solid oral dosage forms in the pharmaceutical industry,sureteric was designed for easy preparation, processing and clean up.

PATENT SEARCH REPORTS[37]

US 2008/0317845 A1

The patent application shows formulation of Duloxetine formulation comprising of core with desired quantity of Duloxetine, a separating layer with HPMC and an enteric coating made with HPMCP

US 2008/0226711 A1

The patent application shows development of Duloxetine formulation comprising of core coated with desired quantity of Duloxetine, a separating layer on the core and an enteric coating made with HPMCP

US 2010/0040680 A1

The patent application shows development of Duloxetine formulation comprising of core coated with desired quantity of Duloxetine, a separating layer on the core and an enteric coating made with different enteric polymers which soluble at different Ph.

US 2009/0226517 A1

The patent application shows development of Duloxetine formulation comprising of core coated with Duloxetine salt form, a separating layer contains an amino acid disposed over the drug layer and an outer enteric coating made HPMCP.

DISEASE PROFILE [38,39]

INTRODUCTION

Depression is a common mental disorder that presents with depressed mood, sad and/or irritable mood exceeding normal sadness or grief loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration. More specifically, the sadness of depression is characterized by a greater intensity and duration and by more severe symptoms and functional disabilities than is normal. Depression occurs in persons of all genders, ages, and backgrounds.

These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities. At its worst, depression can lead to suicide, a tragic fatality associated with the loss of about 850 000 lives every year.

Depression is the leading cause of disability as measured by YLDs and the 4th leading contributor to the global burden of disease (DALYs) in 2000. By the year 2020, depression is projected to reach 2nd place of the ranking of DALYs calcuated for all ages, both sexes. Today, depression is already the 2nd cause of DALYs in the age category 15-44 years for both sexes combined.

Depressive signs and symptoms are characterized not only by negative thoughts, moods, and behaviours but also by specific changes in bodily functions (for example, crying spells, body aches, low energy or libido, as well as problems with eating, weight, or sleeping). The functional changes of clinical depression are often called neurovegetative signs. This means that the nervous system changes in the brain cause many physical symptoms that result in diminished participation and a decreased or increased activity level.

Facts

- Depression is common, affecting about 121 million people worldwide.
- Depression is among the leading causes of disability worldwide.
- Depression can be reliably diagnosed and treated in primary care.
- Fewer than 25 % of those affected have access to effective treatments.

Depression can be reliably diagnosed in primary care. Antidepressant medications and brief, structured forms of psychotherapy are effective for 60-80 % of those affected and can be delivered in primary care. However, fewer than 25 % of those affected (in some countries fewer than 10 %) receive such treatments.

In a major medical study, depression caused significant problems in the functioning of those affected more often than did arthritis, hypertension, chronic lung disease, and diabetes, and in some ways as often as coronary artery disease.

Depression can increase the risks for developing coronary artery disease, HIV, asthma, and many other medical illnesses. Furthermore, it can increase the morbidity (illness/negative health effects) and mortality (death) from these and many other medical conditions.

Depression can coexist with virtually every other mental health illness, aggravating the status of those who suffer the combination of both depression and the other mental illness.

Depression in the elderly tends to be chronic, has a low rate of recovery, and is often undertreated. This is of particular concern given that elderly men, particularly elderly white men have the highest suicide rate.

Physiology or mechanism[40]:

Depression is thought to arise from changes in substances in the brain (neurotransmitters) that help nerve cells communicate, such as serotonin, dopamine and norepinephrine. The levels of these neurotransmitters can be influenced by genetics, hormonal changes, responses to medications, aging, brain injuries, seasonal/light cycle changes, and other medical conditions. The genetic contribution to depression is estimated to be 40-50%. Women are twice as likely as men to experience depression, perhaps because of fluctuations in hormone levels during the menstrual cycle and after childbirth.

The Biogenic Amine Hypothesis states that depression is caused by monoamines, particularly noradrenaline and serotonin.

According to this hypothesis, depression can be alleviated by drugs that increase the availability of noradrenaline and serotonin.

Treatment

Antidepressant drugs are thought to work by increasing the amount of neurotransmitter in the cleft. They do this by blocking metabolism of monoamines - the MAOIs - or by blocking reuptake - the TCAs. Most TCAs are more effective in blocking noradrenaline reuptake than serotonin reuptake.

MAO inhibitors

MAOIs were among the first clinically proven antidepressants. Taken chronically Drugs which block the metabolism of noradrenaline and serotonin via inhibition of MAO are called MAO inhibitors, MAOIs also produce desensitization and down-regulation of postsynaptic receptors. MAO degrades neurotransmitters. When the action of MAO is blocked, neurotransmitters are not metabolised, so they accumulate in the presynaptic neuron

1. Nardil
2. Parnate

Selective serotonin reuptake inhibitors

A **serotonin reuptake inhibitor** (**SRI**) is a type of drug which acts as a reuptake inhibitor for the neurotransmitter serotonin (5-hydroxytryptamine (5-HT)) by blocking the action of the serotonin transporter (SERT). This in turn leads to increased extracellular concentrations of serotonin and therefore an increase in serotonergic neurotransmission. Most commonly used SRI are

1. Lexapro
2. Luvox
3. Paxil
4. Prozac
5. Zoloft

Tricyclic antidepressants or TCAs.

TCAs are effective in blocking the reuptake of noradrenaline and serotonin into the presynaptic neuron, they are non-selective: they also block postsynaptic receptor sites, including cholinergic (muscarinic), histaminergic, and adrenergic receptor sites. Blockade of histaminergic receptors can lead to sedation, weight gain, and hypotension. In the elderly, this is a particular problem, since it can result in fainting or falls. TCAs also block muscarinic receptors, which can lead to blurred vision, dry mouth, constipation, urinary retention, confusion, and delirium, some of the most commonly used TCAs are.

1. Anafranil
2. Elavil
3. Endep

4. Ludiomil
5. NorpraminPamelor
6. Pertofrane
7. Sinequan
8. Surmontil
9. Tofranil
10. Vivactil

Serotonin-noradrenaline reuptake inhibitors (SNRIs)

The Permissive Hypothesis postulates that low levels of serotonin permit abnormal levels of noradrenaline to cause depression or mania. If serotonin cannot control noradrenaline, and noradrenaline falls to abnormally low levels, the patient becomes depressed. On the other hand, if the level of serotonin falls and the level of noradrenaline become abnormally high, the patient becomes manic.

According to this hypothesis, antidepressant drugs are effective to the degree that they reinstate the ability of serotonin to control noradrenaline, thus restoring the critical balance that controls emotional behavior.

A new class of antidepressant drugs, work to selectively block reuptake of both noradrenaline and serotonin, thereby increasing levels of both monoamines. The SNRIs have very little affinity for other postsynaptic receptor sites and are therefore less likely to produce some of the side effects associated with TCAs some of the most commonly used SNRIs are.

1. Cymbalta
2. Effexor
3. Pristiq

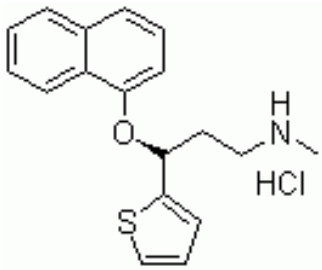
DRUG PROFILE[41,42,18,40]

Duloxetine is included in the class of drugs called selective serotonin/ norepinephrine reuptake inhibitors (SNRIs). which is used to treat depression, anxiety, and other mood disorders.

Name **:** Duloxetine hydrochloride

Synonyms: N-Methyl-gama-(1-naphthalenyloxy)-2-thiophenepropanamine

Molecular Structure:



Molecular Formula **:** $C_{18}H_{19}NOS \cdot HCl$

Molecular Weight **:** 333.88 g/mol

IUPAC **:** (+)-(S)-N-Methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine

Mode of action:

Duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake.

Pka	**:**	9.34
Half Life	**:**	**12 hours (range 8-17 hours)**
Absorption	**:**	Orally administered duloxetine hydrochloride is well absorbed
BCS Classification	**:**	CLASS II (Low solubility high permeability)
Storage	**:**	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F
Bioavailability	**:**	80% (32% to 80%)
Protein binding	**:**	95%
Excretion	**:**	70% in urine, 20% in feces
Dosage Forms	:	Capsule, coated pellets
Toxicity	**:**	Oral, rat LD_{50}: 491 mg/kg for males and 279 mg/kg for females. Symptoms of overdose include tremors, convulsions, reduced activity, slow pupillary response, intermittent tremors, and rigidity.

Pharmacology[42]

Duloxetine is in a class of medications called selective serotonin and norepinephrine reuptake inhibitors (SSNRIs) and primarily targets major depressive disorders (MDD) and stress urinary incontinence (SUI). Duloxetine is also used to treat pain and tingling caused by diabetic neuropathy (damage to nerves that can develop in people who have diabetes).it is a potent dual inhibitor of serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE) reuptake, possessing comparable affinities in binding to NE and 5-HT transport sites. Interestingly, its behaviour contrasts to most other dual-reuptake inhibitors. Furthermore, duloxentine lacks affinity for monoamine receptors within the central nervous system.

Duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors. The antidepressant and pain inhibitory actions of duloxetine are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.

Indications[18]

The main uses of duloxetine are in major depressive disorder, general anxietydisorder, stress urinary incontinence, painful peripheral neuropathy and fibromyalgia. In addition, it is being studied for various other indications.

Mechanism of Action[18]

Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.

Pharmacodynamics[18]

Preclinical studies have shown that duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors in vitro. Duloxetine does not inhibit monoamine oxidase (MAO).

Pharmacokinetics[18]

Duloxetine has an elimination half-life of about 12 hours (range 8 to 17 hours) and its pharmacokinetics is dose proportional over the therapeutic range. Steady-state plasma concentrations are typically achieved after 3 days of dosing.

Elimination of duloxetine is mainly through hepatic metabolism involving two P450 isozymes, CYP1A2 and CYP2D6.

Absorption and Distribution:

Orally administered duloxetine hydrochloride is well absorbed. There is a median 2 hour lag until absorption begins (Tlag), with maximal plasma concentrations (Cmax) of duloxetine occurring 6 hours post dose. Food does not affect the Cmax of duloxetine, but delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 10%. There is a 3 hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared to a morning dose.

The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (> 90%) to proteins in human plasma, binding primarily to albumin and α1-acid glycoprotein. The interaction between duloxetine and other highly protein bound drugs has not been fully evaluated. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment.

Metabolism and Elimination[43]

Biotransformation and disposition of duloxetine in humans have been determined following oral administration of 14C-labeled duloxetine. Duloxetine comprises about 3% of the total radiolabeled material in the plasma, indicating that it undergoes extensive metabolism to numerous metabolites. The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring followed by conjugation and further oxidation. Both CYP1A2 and CYP2D6 catalyze the oxidation of the naphthyl ring in vitro. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate. Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (< 1% of the dose) amounts of unchanged duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites of duloxetine; about 20% is

excreted in the feces. Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine.

STABILITY DATA[37]

Duloxetine molecule decomposes easily in an acidic environment upon formation of a highly toxic naphthol moiety, 60% of API gets degraded in 30min of contact with acid.

Some degradation product of duloxetinme include "α-napthol', "4 -napthol Duloxetine", "3 -acetyl Duloxetine"

The acid degradation of drug data shows that, if the drug reaches the stomach in an acidic pH, the drug will easily get decomposed result in the formation of toxic substance and reduced bioavailability. Thus the drug should be formulated in such a way that it bypasses the gastric fluid and release in small intestine. So as to target the small intestine a delayed release formulation has selected.

EXCIPIENT PROFILE[44]

LACTOSE MONOHYDRATE

Nonproprietary Names

BP : Lactose monohydrate

JP : Lactose

PhEur : Lactosummonohydricum

USPNF : Lactose monohydrate

Synonyms

Lactose Monohydrate NF, Lactochem coarse crystals, lactochem powder, pharmatose DCL 15, pharmatose 50M, HMS coarse powder, NF lactose 310, Granulac 70, prismalac 40, Inhalac 70 etc.

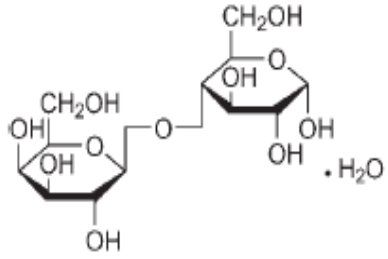
Empirical Formula

$C_{12}H_{22}O_{11}.H_2O$

Molecular Weight

360.31

Structural Formula



α-Lactose monohydrate

Description

In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. α-lactose monohydrate, β-lactose anhydrous, and α-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α -lactose is approximately 20 % as sweet as sucrose, while β-lactose is 40 % as sweet.

Functional Category

Binding agent; diluent for dry-powder inhalers; tablet binder; tablet and capsule diluent.

Applications in Pharmaceutical Formulation or Technology

1. Lactose is widely used as filler or diluents in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas.
2. Lactose is also used as diluents in dry-powder inhalation. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics.
3. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently.
4. Other applications of lactose include use in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid cohesion.
5. Lactose is also used in combination with sucrose (approximately 1:3) to prepare sugar-coating solutions. Direct-compression grades of lactose monohydrate are available as granulated/agglomerated a-

lactose monohydrate, containing small amounts of anhydrous lactose.

6. Direct-compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation. Other directly compressible lactoses are spray-dried lactose and anhydrous lactose.

Stability and Storage Conditions

Mold growth may occur under humid conditions (80 % relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions; the purities of different lactose can vary and color evaluation may be important, particularly if white tablets are being formulated. The color stabilities of various lactoses also differ. Lactose should be stored in a well-closed container in a cool, dry place.

Incompatibilities

A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. Lactose is also incompatible with amino acids, aminophylline, amphetamines, and lisinopril.

HYDROXY PROPYL METHYL CELLULOSE

Nonproprietary Names

BP : Hypromellose

JP : Hypromellose

PhEur : Hypromellose

USP : Hypromellose

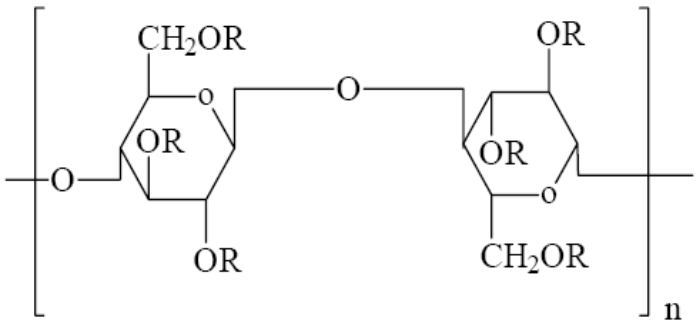
Synonyms

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

Molecular Weight

Molecular weight is approximately 10,000-1,50,0000.

Structural Formula



Where R is H, CH_3, or CH_3CH (OH) CH2

Description

Hypromellose is an odorless and tasteless, white or creamywhite fibrous or granular powder.

Functional Category

Bioadhesive material; coating agent, controlled-release agent, dispersing agent, dissolution enhancer, emulsifying agent, emulsion stabilizer extended-release agent; film-forming agent, foaming agent, granulation aid modified-release agent, mucoadhesive, release-modifying agent, solubilizing agent, stabilizing agent, suspending agent, sustained-release agent, tablet binder, thickening agent, viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

1. Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations.
2. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0 %. Hypromellose produces aqueous solutions of greater clarity, with fewer undissolvedfibers present, and is therefore preferred in formulations for ophthalmic use.
3. Hypromellose is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses.

Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point is 50–90^{0}C, depending upon the grade and concentration of material. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is non-ionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

SODIUM STARCH GLYCOLATE

Synonyms

Carboxymethyl starch, Explotab, Primojel.

Functional Category

Tablet and capsule disintegrant.

Description

It is white to off-white, odourless, tasteless, free-flowing powder.

Incompatibilities

Incompatible with ascorbic acid

Stability and Storage

It is a stable material. It should be stored in a well closed container to protect from wide variations in humidity and temperature that may cause cracking.

Applications in Pharmaceutical Formulation and Technology

As a disintegrant in tablet (wet granulation and direct compression) and capsule formulation in 2-8% concentration.

Micro Crystalline Cellulose

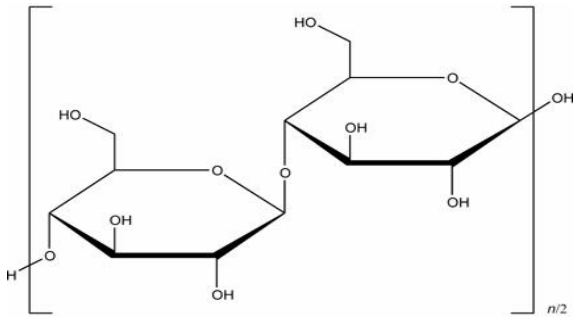
Non Proprietary Names

BP	:	Microcrystalline Cellulose
JP	:	Microcrystalline Cellulose
PhEur	:	Cellulose, Microcrystalline
USP-NF	:	Microcrystalline Cellulose

Synonyms

Avicel PH; Celex; Cellulose gel; hellulosummicrocristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; ethispheres

Structural Formula



Description

Microcrystalline cellulose is a purified partially depolymerised cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ 36000

where n = 220

Functional Category

Adsorbent, suspending agent, tablet and capsule, diluents, tablet disintegrant.

Stability and Storage Conditions

Microcrystalline cellulose is a stable through hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Microcrystalline cellulose is a incompatible with strong oxidizing agents.

Applications

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluents in oral tablet and capsule formulations where it is used in both wet granulation and direct-compression processes. In addition to its use as a binder/diluents, microcrystalline cellulose also has some lubricant and disintegrantproperties that make it useful in tableting.

MAGNESIUM STEARATE

Synonyms:

Stearic acid magnesium salt, magnesium salt, magnesium octadecanoate

Description:

It is a fine, white, precipitated of milled, impalpable powder of low bulk density, having a faint odor of stearic acid & a characteristic taste.

Structural Formula:

$[CH_3(CH_2)_{16}COO]_2Mg$

Empirical Formula & Molecular Weight:

$C_{36}H_{70}MgO_4$; 591.34

Solubility:

It is insoluble in water, ethanol & ether, slightly soluble in warm benzene & warm ethanol

Functional categories:

Tablet & capsule lubricant

Storage:

Should be stored in well-closed container in a cool, dry place. It is stable compound.

Incompatibilities:

Incompatible with strong oxidizing agents, strong acids, alkalis &iron salts. It cannot be used in products containing aspirin, some vitamins, & mostalkaloidal salts.

Applications:

Used in cosmetics, food & pharmaceutical formulations and as a lubricant capsule &table at concentration between 0.25-5.0%.

Ethylcellulose

Nonproprietary Names

BP : Ethylcellulose

PhEur : Ethylcellulosum

USPNF : Ethylcellulose

Synonyms

Aquacoat ECD; Aqualon; E462; Ethocel;Surelease.

Empirical Formula and Molecular Weight

Ethylcellulose with complete ethoxyl substitution (DS = 3) is C12H23O6(C12H22O5)nC12H23O5 where n can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is along-chain polymer of b-anhydroglucose units joined together by acetal linkages.

Functional Category

Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Ethylcellulose is widely used in oral and topical pharmaceuticalformulations; The main use of ethylcellulose in oral formulations is as ahydrophobic coating agent for tablets and granules.

Ethylcellulose coatings are used to modify the release of adrug,(7–10) to mask an unpleasant taste, or to improve thestability of a formulation; for example, where granules arecoated with ethylcellulose to inhibit oxidation. Modified release tablet formulations may also be produced using ethylcellulose as a matrix former.

Ethylcellulose, dissolved in an organic solvent or solventmixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility,(15) by the addition of hypromellose(16) or a plasticizer;(17–19) see Section 18. Anaqueous polymer dispersion (or latex) of ethylcellulose such as Aquacoat ECD (FMC Biopolymer) orSurelease (Colorcon) may also be used to produce ethylcellulose films without theneed for organic solvents. Drug release through ethylcellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets orgranules compared with tablets) is utilized. In those instances, aqueous ethylcellulose dispersions are generally used to coat granules or

pellets. Ethylcellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression.

Stability and Storage Conditions

Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both diluteand concentrated, and to salt solutions, although it is more sensitive to acidic materials than are celluloseesters. Ethylcellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemicaladditives that absorb light in the 230–340nm range. Ethylcellulose should be stored at a temperature notexceeding 328C (908F) in a dry area away from all sources of heat. It should not be stored next toperoxides or other oxidizing agents.

Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

Talc

Nonproprietary Names

BP : Purified talc

JP : Talc

PhEur : Talcum

USP : Talc

Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; MagsilOsmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

Empirical Formula and Molecular Weight

Talc is a purified, hydrated, magnesium silicate, approximating to the formula Mg6(Si2O5)4(OH)4. Itmay contain small, variable amounts of aluminum silicate and iron.

Functional Category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products.Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets;and as an adsorbant.

In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves; Talc is a natural material; it may therefore frequently contain microorganisms andshould be sterilizedwhen used as a dusting powder;Talc is additionally used to clarifyliquids and is also used incosmetics and food products, mainly for its lubricant properties.

Description

Talc is a very fine, white to greyish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness

Stability and Storage Conditions

Talc is a stable material and may be sterilized by heating at 1608C for not less than 1 hour. It may also besterilized by exposure to ethylene oxide or gamma irradiation.(10) Talc should be stored in a well-closedcontainer in a cool, dry place.

Incompatibilities

Incompatible with quaternary ammonium compounds.

Triethyl Citrate

Nonproprietary Names

BP : Triethyl citrate

PhEur : Triethyliscitras

USPNF : Triethyl citrate

Synonyms

Citric acid, ethyl ester; Citroflex 2; Citrofol AI; E1505; Hydagen CAT; TEC.

Empirical Formula and Molecular Weight

C12H20O7 276.29

Functional Category

Plasticizer.

Applications in Pharmaceutical Formulation or Technology

Triethyl citrate and the related esters acetyltriethyl citrate, tributyl citrate, and acetyltributyl are used to plasticize polymers in formulated pharmaceutical coatings. The coating applications include capsules, tablets, beads, and granules for taste masking, immediate release, sustainedrelease,and enteric formulations. Triethyl citrate is also used as a direct food additive forflavoring, for solvency, and as a surface active agent.

Description.

Triethyl citrate is a clear, odorless,practically colorless, oily liquid.

Stability and Storage Conditions

Triethyl citrate should be stored in a closed container in a cool, dry location. When stored in accordancewith these conditions, triethyl citrate is a stable product.

Incompatibilities

Triethyl citrate is incompatible with strong alkalis and oxidizing materials.

POLYMETHACRYLATES

Nonproprietary Names

BP: Methacrylic acid-ethyl acrylate copolymer (1 : 1)

PhEur: Acidummethacrylicum et ethylisacrylaspolymerisatum1 : 1

Acidummethacrylicum et ethylisacrylaspolymerisatum1 : 1 dispersio 30 per centum

Acidummethacrylicum et methylismethacrylaspolymerisatum1 : 1

Acidummethacrylicum et methylismethacrylaspolymerisatum1 : 2

CopolymerummethacrylatisbutylatibasicumPolyacrylatis dispersion 30 per centum

USPNF: Ammonio methacrylate copolymer

Methacrylic acid copolymer

Methacrylic acid copolymer dispersion

Synonyms

Acryl-EZE; Acryl-EZE MP; Eastacryl 30D; Eudragit; Kollicoat MAE 30 D; Kollicoat MAE 30 DP; polymeric methacrylates.

Molecular weight:

Typically, the molecular weight of the polymer is-5,10,0000.

Functional Category

Film-forming agent, tablet binder, tablet diluents.

Applications in Pharmaceutical Formulation or Technology

Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents. Depending on the type of polymer used, films of different solubility characteristics can be produced; Eudragit E is used as a plain or insulating film former. It is soluble in gastric fluid below pH 5. In contrast, Eudragit L, S and FS types are used as enteric coating agents because they are resistant to gastric fluid. Eudragit RL, RS, NE 30D, NE 40D, andNM30D are used to form water-insoluble film coats for sustained-release products. Eudragit RL films are more permeable than those of Eudragit RS, and films of varying permeability can be obtained by mixing the two types together. Eudragit L 30 D-55 is used as an enteric coating film former for solid-dosage forms. The coating is resistant to gastric juice but dissolves readily at above pH 5.5. Eudragit L 100-55 is an alternative to Eudragit L 30 D-55. It is commercially available as a redispersible powder.

Stability and Storage Conditions

Dry powder polymer forms are stable at temperatures less than 3080C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance and the clumps can readily be broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 3080C.

Dispersions are sensitive to extreme temperatures and phase separation occurs below 00C. Dispersions should therefore be stored at temperatures between 5 and 2580C and are stable for at least 18 months after shipping from the manufacturers warehouse if stored in a tightly closed container at the aboveconditions.

Incompatibilities

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be causedby soluble electrolytes, pH changes, some organic solvents, and extremes of temperature; For example, dispersions of Eudragit L 30 D, RL 30 D, L 100-55, and RS 30 D are incompatible with magnesium stearate. Eastacryl 30D, Kollicoat MAE 30 D, and Kollicoat MAE 30 DP are also incompatible with magnesium stearate. Interactions between polymethacrylates and some drugs can occur, although solid polymethacrylates and organic solutions are generally more compatible than aqueous dispersions.

POVIDONE K-30

Synonyms:

Kollidon,Plasdone,polyvinylpyrrolidone,

Empirical Formula and Molecular Weight:

(C6H9NO)n& 50,000

Functional Category:

Disintegrant, Dissolution enhancer, Suspending agent, Tablet binder.

Applications in Pharmaceutical Formulation or Technology:

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

Description:

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic.

Stability and Storage Conditions:

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities:

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals.

Hydroxypropyl Cellulose

Nonproprietary Names

BP	:	Hydroxypropylcellulose
JP	:	Hydroxypropylcellulose
PhEur	:	Hydroxypropylcellulosum
USPNF	:	Hydroxypropyl cellulose

Synonyms

Cellulose, hydroxypropyl ether; E463; hyprolose; Klucel;Methocel; Nisso HPC; oxypropylated cellulose.

Empirical Formula and Molecular Weight

The PhEur 2005 and USPNF 23 describe hydroxypropylcellulose as a partially substituted poly(hydroxypropyl) etherof cellulose. It may contain not more than 0.6% of silica or another suitable anticaking agent. Hydroxypropyl cellulose iscommercially available in a number of different grades thathave various solution viscosities. Molecular weight has a range of 50 000–1 250 000.

Functional Category

Coating agent; emulsifying agent; stabilizing agent; suspendingagent; tablet binder; thickening agent; viscosity-increasingagent.

Applications in Pharmaceutical Formulationor Technology

Hydroxypropyl cellulose is widely used in oral and topicalpharmaceutical formulations, In oral products, hydroxypropyl cellulose is primarily usedin tableting as a binder,(1) film-coating,(2) and extended-releasematrixformer.(3–5) Concentrations of hydroxypropyl cellulose of 2–6% w/w may be used as a binder in either wet-granulationor dry, direct-compression tableting processes.(6–10) Concentrationsof 15–35% w/w of hydroxypropyl cellulose may be usedto produce tablets with an extended drug release. Therelease rate of a drug increases with decreasing viscosity ofhydroxypropylcellulose.In topical formulations,hydroxypropyl cellulose is used in transdermal patches andophthalmic preparations. Hydroxypropyl cellulose is also used in cosmetics and infood products as an emulsifier and stabilizer.

Description

Hydroxypropyl cellulose is a white to slightly yellow-colored,odorless and tasteless powder.

Stability and Storage Conditions

Hydroxypropyl cellulose powder is a stable material, althoughit is hygroscopic after drying.

Aqueous solutions of hydroxypropyl cellulose are stable atpH 6.0–8.0, with the viscosity of solutions being relativelyunaffected. However, at low pH aqueous solutions may undergo acid hydrolysis, resulting in chain scission and hencea decrease in solution viscosity. The rate of hydrolysis increaseswith increasing temperature and hydrogen ion concentration.

At high pH, alkali-catalyzed oxidation may degrade thepolymer and result in a decrease in viscosity of solutions.Hydroxypropyl cellulose powder should be stored in a wellclosed container in a cool, dry place.

Incompatibilities

Hydroxypropyl cellulose in solution demonstrates someincompatibility with substituted phenol derivatives, such asmethylparaben and propylparaben. The presence of anionic polymers may increase the viscosity of hydroxypropyl cellulosesolutions.

The compatibility of hydroxypropyl cellulose with inorganicsalts varies depending upon the salt and its concentration

Sodium Alginate

Nonproprietary Names

BP : Sodium alginate

PhEur : Natriialginas

USPNF : Sodium alginate

Synonyms

Algin; alginic acid, sodium salt; E401; Kelcosol; Keltone; Protanal; sodium polymannuronate.

Empirical Formula and Molecular Weight

Sodium alginate consists chiefly of the sodium salt of alginicacid, which is a mixture of polyuronic acids composed ofresidues of D-mannuronic acid and L-guluronic acid.

Functional Category

Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Sodium alginate is used in a variety of oral and topicalpharmaceutical formulations.(2) In tablet formulations, sodiumalginate may be used as both a binder and disintegrant;(3) it has been used as a diluent in capsule formulations.Sodiumalginate has also been used in the preparation of sustainedreleaseoral formulations since it can delay the dissolution of a drug from tablets,capsules, and aqueous suspensions.In topical formulations, sodium alginate is widely used as athickening and suspending agent in a variety of pastes, creams,and gels, and as a stabilizing agent for oil-in-water emulsions.

Description

Sodium alginate occurs as an odorless and tasteless, white topale yellowish-brown colored powder.

Stability and Storage Conditions

Sodium alginate is a hygroscopic material, although it is stableif stored at low relative humidities and a cool temperature.Sodium alginate solutions are susceptible on storage to microbial spoilage, which may affect solution viscosity.Solutions are ideally sterilized using ethylene oxide, althoughfiltration using a 0.45 mm filter also has only a slight adverse effect on solution viscosity

Incompatibilities

Sodium alginate is incompatible with acridine derivatives,crystal violet, phenylmercuric acetate and nitrate, calcium salts,heavy metals, and ethanol in concentrations greater than 5%.

Low concentrations of electrolytes cause an increase in viscositybut high electrolyte concentrations cause salting-out of sodiumalginate; salting-out occurs if more than 4% of sodium chlorideis present

Hypromellose Acetate Succinate

Nonproprietary Names

USPNF: Hypromellose acetate succinate

Synonyms

Aqoat; Aqoat AS-HF/HG; Aqoat AS-LF/LG; Aqoat AS-MF/

MG; cellulose, 2-hydroxypropyl methyl ether, acetate succinate;

HPMCAS.

Empirical Formula and Molecular Weight

Hypromellose acetate succinate is a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethyl cellulose.

The molecular weight of hypromellose acetate succinate is approximately 55 000–93 000 Daltons.

Functional Category

Component of controlled-release or sustained-release dosage forms; enteric coating agent; film-forming agent; solid dispersion vehicle.

Applications in Pharmaceutical Formulation or Technology

Hypromellose acetate succinate is commonly used in oral pharmaceutical formulations as a film coating, as well as enteric coating material for tablets or granules.(5–7) It is insoluble in gastric fluid but will swell and dissolve rapidly in the upper intestine. For aqueous film-coating purposes, a dispersion of hypromellose acetate succinate fine powder and triethyl citrate (as a plasticizer) in water is commonly utilized.(4,8,9) Organic solvents can also be used as vehicles for applying this polymer as a film coating.

Description

Hypromellose acetate succinate is a white to off-white powder or granules.(4) It has a faint acetic acid-like odor and a barely detectable taste. Hypromellose acetate succinate is available in several grades, according to the pH at which the polymer dissolves (low, L; medium, M; and high, H) and its predominant particle size (cohesive fine powder, F; or freeflowing granules, G).

Stability and Storage Conditions

Hypromellose acetate succinate should be stored in a wellclosed container, in a cool, dry place. In such storage conditions, hypromellose acetate succinate is a stable material.

It is stable for four years after manufacturing. Hypromellose acetate succinate is hygroscopic. It is hydrolyzed to acetic acid and succinic acid, and the hypromellose polymer starts to form if dissolved in 1 mol/L sodium hydroxide for more than twohours. The hydrolysis is the main degradation pathway that is responsible for increasing amounts of free acids in storage, especially upon exposure to moisture.Hypromellose Acetate Succinate

Incompatibilities

Hypromellose acetate succinate is incompatible with strong acids or bases, oxidizing agents, and sustained levels of elevated humidity.

SUITABILITY OF DRUG

1. Duloxetine is a selective serotonin/nor-epinephrine reuptake inhibitor (SNRI) which is used to treat depression, anxiety, and other mood disorders.
2. Duloxetine Hydrochloride is acid instable drug; it degrades rapidly in acidic environment to form its inactive and toxic metabolites.
3. So to make drug better available in body and to decrease its degradation and impurity levels the drug must be formulated as a delayed release formulation to improve its bioavailability.
4. Multiparticulate systems-Because of their smaller particle size compared to single unit dosage forms these systems are capable of passing through the upper GI tract easily, and reach the intestine quickly and retained longer time thus, a multiparticulate system of delayed release formulation is suitable for Duloxetine Hydrochloride.
5. Programmable oral drug absorption system (PRODAS) is a type of multiparticulate system, where a number of mini tablets filled in hard gelatin capsule. Thus it combines the benefits of tableting technology within a capsule. Compared to other multiparticulate systems (for ex: pellets) production of mini tablets is as simple as conventional tablets and it is economic, low cost production, no need of advanced technology & trained personals, though we can get the same benefits as that of pellets, thus a programmable oral drug absorption system (mini tablets) of delayed release formulation is suitable for Duloxetine Hydrochloride.

AIM AND OBJECTIVE OF WORK

The aim of the present study is to develop and evaluate a delayed release oral capsule comprising Duloxetine Hydrochloride mini tablets 60mg strength with various enteric coating polymers with the following objectives

1. To study the Drug-Excipient compatibility.
2. To minimize the drug release in stomach (acidic environment) thereby reduce the formation of metabolite and increase the bioavailability.
3. To develop a formulation which is similar in dissolution profile and there by establishing similarity to that of the reference product CYMBALTA
4. To develop a cost effective medicine when compare to marketed product.
5. To improve patient compliance.

PLAN OF WORK

1. Collection of innovator product details
2. To carry out the pre formulation studies of API.
    a. Description
    b. Bulk density, Tapped density.
    c. Flow properties
    d. Angle of repose
    e. Car's index
    f. Hausner's ratio
    g. Particle size distribution by mechanical sieve shaker.
    h. Solubility studies (pH solubility profile)
    i. Water content by Karl Fisher method
    j. Moisture pickup study
    k. Drug-Excipient compatibility study by FT-IR
3. Analytical method development
    a. Determination of ʎmax.
    b. Determination of calibration curve.
4. To take batches to optimize the formulation ingredients and develop final formulation.

    Steps involved in formulation development of Duloxetine Hcl DR capsules

Step-I: Compression of core mini tablets..

Step-II: Barrier coating of core mini tablets

Step-III: Enteric coating

5. Results and discussion

6. Conclusion.

MATERIALS & METHODS

Table No.2 List of Excipients used

S.NO	INGREDIENTS	CATEGORY
1	Minrocrystalline cellulose PH102	Diluent
2	Lactose mono hydrate	Diluent
3	Klucel	Binder
4	Sodium starch glycolate	Disintegrent
5	Magnesium stearate	Lubricant
6	HPMC 3cps	Binder
7	Talc	Opacifier
8	Purified water	Solvent
9	Acryleze MP	Enteric coating polymer
10	PVP K30	Binder
11	HPMC AS MF	Enteric coating polymer
12	TEC	Placticizer
13	NS enteric	Enteric coating polymer
14	Surelase	Enteric coating polymer

Instrument and Apparatus used

Table No.3 List of Instruments used

S.NO	INSTRUMENT	MAKE
1	COATING PAN	SAMS TECHNOMECH
2	DIGITAL WEIGHING BALANCE	SHIMADZU
3	SHIFTER	SAMS TECHNOMECH
4	ROTARY COMPRESSION MACHINE	CADMECH
5	FRIABILATOR	ELECTROLAB
6	VERNIER CALIPER	MITUTIYO
7	MECHANICAL STIRRER	REMI MOTOR
8	HARDNESS TESTER	VARIAN
9	DISINTEGRATION TEST APPARATUS	ELCTROLAB
10	TRAY DRYER	GANSONS
INSTRUMENT USED IN ANALYSIS		
1	PH METER	THERMOORION
2	DISSOLUTION APPARATUS	ELECTROLAB
3	UV APPARATUS	SHIMADZU
4	SONICATOR	ENERTECH

METHODS USED

1. Compression of core mini tablets

   The direct compression method has been selected for compression of core mini tablets as it is simple, easy, convenient, suitable and more economic.

2. Dissolution Studies (pH dissolution profiling)

   Based on the pharmacokinetics and physico-chemical characteristics of the API the following dissolution method was selected for the reference product characterisation and further product development.

A. Gastric challenge:

   USP I, 100 rpm, 1000ml 0.1N HCl for 2 hours and the mini tablets were assayed for drug content.

B. Dissolution (0.1N HCl followed by pH 6.8 Phosphate buffer)

   USP I, 100 rpm, 1000ml 0.1N HCl for 2 hours followed by 1000ml pH 6.8 Phosphate buffer, sampling at 15, 30, 45, 60, 90 and 120 min.

Dissolution media preparation:

a) 0.1N Hydrochloric acid USP

   8.5 g of concentrated hydrochloric acid is made up to 1000 ml with purified water.

b) pH 6.8 Phosphate buffer USP

   6.8 gm of potassium dihydrogen phosphate is mixed with 1000ml of water and the pH was adjusted to 6.8 using dilute NaOH solution.

EXPERIMENTATION

PRE FORMULATION STUDIES

1. Description

Duloxetine Hydrochloride is a white to off white powder

2. Bulk Density

Duloxetine Hydrochloride was analyzed for apparent and tap density. This was determined by using Erweka Tap density apparatus. Results are presented below.

Table No 4: Bulk Density

Bulk Density (gm/cc)	0.220
Tap Density (gm/cc)	0.460

3. Solubility Studies (pH Solubility profile)

Solubility of Duloxetine Hydrochloride was analyzed in various media at different pH. The data is presented below.

Table No 5: Solubility Profile

Medium	Solubility (mg/ml)	Quantity/250ml
Purified Water	50.40	12.60 gm
0.001N Hydrochloric acid	53.70	13.42 gm
pH 4.5 Acetate buffer	57.92	14.48 gm
pH 5.5 Acetate buffer	110.23	27.55 gm
pH 6.8 Phosphate buffer	4.25	1.06 gm

Above data shows that quantity of drug dissolved in 250ml media is more than the highest dose, 60mg. Hence, Duloxetine Hydrochloride can be classified as 'Highly soluble' across all the pH ranges as per the BCS.

4. Particle Size Distribution

Particle size analysis was determined by using laser diffraction method and the results are presented below Instrument used: Malvern apparatus

Table No 6: Particle Size Distribution

Batch Number	DTMU080004	DTMU080005
D_{50}	6µm	6µm
D_{90}	15µm	16µm

5. Water content by Karl Fisher Method:

Water content of two different batches of Duloxetine Hydrochloride was determined by Karl fisher titration and the results are presented below.

Table No 7: Water Content of API

Batch Number	Water by KF
DTMU080001	0.18(%w/w)
DTMU080002	0.22(%w/w)

6. Moisture Pick up Study:

Moisture pickup study of API was carried out at different relative humidity conditions maintained at 25±2°C. Moisture sorption at different humidity conditions was determined by weight method

Table No 8: Moisture Pick up Study

Time (hours)	Condition		
	43%RH	60%RH	75%RH
	% Sorption		
4	-0.03	0.01	0.02
16	-0.08	0.00	0.04
24	-0.11	-0.01	0.05
48	-0.11	-0.02	0.05
72	-0.11	-0.01	0.05

The results reveals that the API has not picked any moisture thus it is concluded that Duloxetine hydrochloride is non hygroscopic

7 carrs index:

Compressiblity is the ability of the Powder to decrease in volume under pressure. Using untapped density. The percentage compressibility was determind which is given as cars compressibility Index.

CI = Vi – V0/Vi x 100

Where CI = Compressibility Index

V0 = Bulk density

Vi = Tapped density

Compressibility Index = 52.17

8 Hausner Ratio

It is measurement of frictional resistance of the drug. It was determind by the ratio of tapped density & bulk density.

Hausner Ratio = $\frac{V0}{Vi}$

where $\frac{V0}{Vi}$ = bulkdensity /tapped density

9 Angle of reporse

Angle of reporse is the maximum angle formed between the surface of pile of powder and horizontal plane. It is usually determined by fixed funnel method and is the ability to measure the flowability of powder

$\theta = \tan^{-1} (h/r)$

H =height of the heap of the pile

R= radius of the base of the pile

Angle of Reporse =44.6

10. Drug excipient compatibility:

The drug excipient compatibility was performed for 4 weeks at 40±2°C/ 75±5% RH. The samples were packed in self seal poly bag. The list of excipients taken & its corresponding ratio were given in the table below.

Table No 9: Drug excipient ratio

S NO	DRUG + EXCIPIENTS	RATIO
1	Duloxetine hydrochloride (API)	1:1
2	API + Micro crystalline cellulose	1:1
3	API + Lactose	1:1
4	API + Eudragit L100 55	1:1
5	API + HPMC Acetate succinate	1:1
6	API + Sodium starch glycolate	1:1
7	API + Talc	1:1
8	API + Magnesium. Stearate	1:1
9	API + Tri Ethyl Citrate	1:1
10	API + Povidone	1:1
11	API + Hydroxy propyl cellulose	1:1
12	API + Hydroxy propyl methyl cellulose	1:1
13	API + NS enteric	1:1
14	API + Surelase	1:1

Table No 10: Drug excipient compatibility

S NO	composition		Physical observation	Water by K/F
1	Duloxetine hydrochloride (API)	Initial	White powder	0.35
		4W 40°C/75	No change	0.37
2	API + Micro crystalline cellulose	Initial	White powder	4.72
		4W 40°C/75	No change	4.62
3	API + Lactose	Initial	White powder	4.44
		4W 40°C/75	Dull colour	4.39
4	API + Eudragit L100 55	Initial	White powder	3.63
		4W 40°C/75	Pink colour	3.59
5	API + HPMC AS	Initial	White powder	2.17
		4W 40°C/75	Ash colour	2.41
6	API + HPMC E5 LV	Initial	White powder	3.70
		4W 40°C/75	No change	4.05
7	API + Sodium starch glycolate	Initial	White powder	3.12
		4W 40°C/75	No change	4.65
8	API + Talc	Initial	White powder	0.35
		4W 40°C/75	No change	0.61
9	API + Magnesium Stearate	Initial	White powder	1.64
		4W 40°C/75	No change	1.74
10	API + Tri Ethyl Citrate	Initial	White paste	0.58
		4W 40°C/75	No change	0.97
11	API + Povidone	Initial	White powder	0.28
		4W 40°C/75	No change	1.24
12	API + Hydroxy propyl cellulose	Initial	White powder	0.12
		4W 40°C/75	No change	1.23
13	API + NS Enteric	Initial	White powder	0.11
		4W 40°C/75	No change	1.35
14.	API + Surelase	Initial	White powder	0.17
		4W 40°C/75	No change	1.27

ANALYTICAL METHOD DEVLOPMENT

DETERMINATION OF λ max:

Preparation of stock solution: 1mg/ml stock solution of Duloxetine hydrochloride is prepared by dissolving 100mg in 100 ml of pH 6.8 phosphate buffer. A 3 µg/ml test solution is prepared and the maximum absorbance is checked from 400-200nm.

The λ max is found to be 218nm.

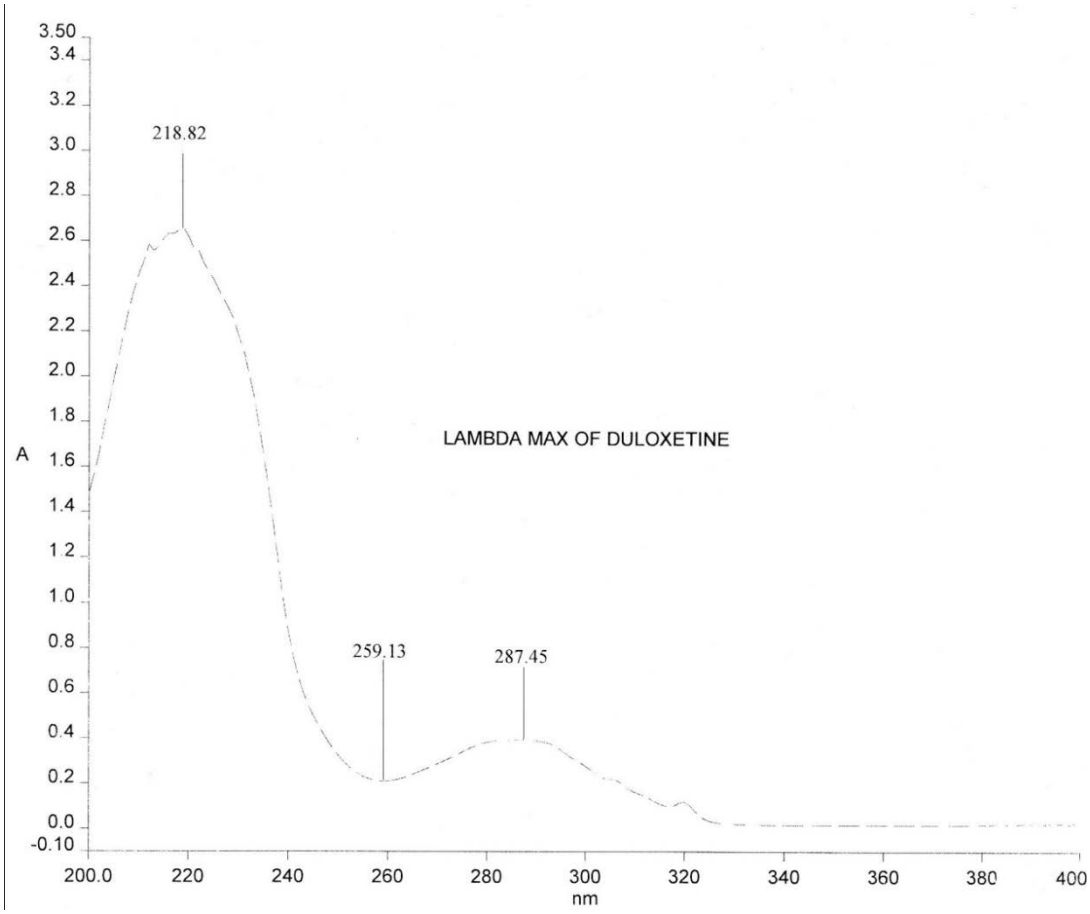


Fig 9 λ max of duloxetine

DETERMINATION OF CALIBRATION CURVE:

A series of test solution containing 1µg/ml, 2µg/ml, 3µg/ml, 4µg/ml,5µg/ml of Duloxetine hydrochloride is prepared using the above stock solution and the absorbance was checked at 218 nm

Table No 11: Calibration Curve

CONCENTRATION	ABSORBENCE
0	0
1	0.1997
2	0.3784
3	0.5647
4	0.7584
5	0.9247

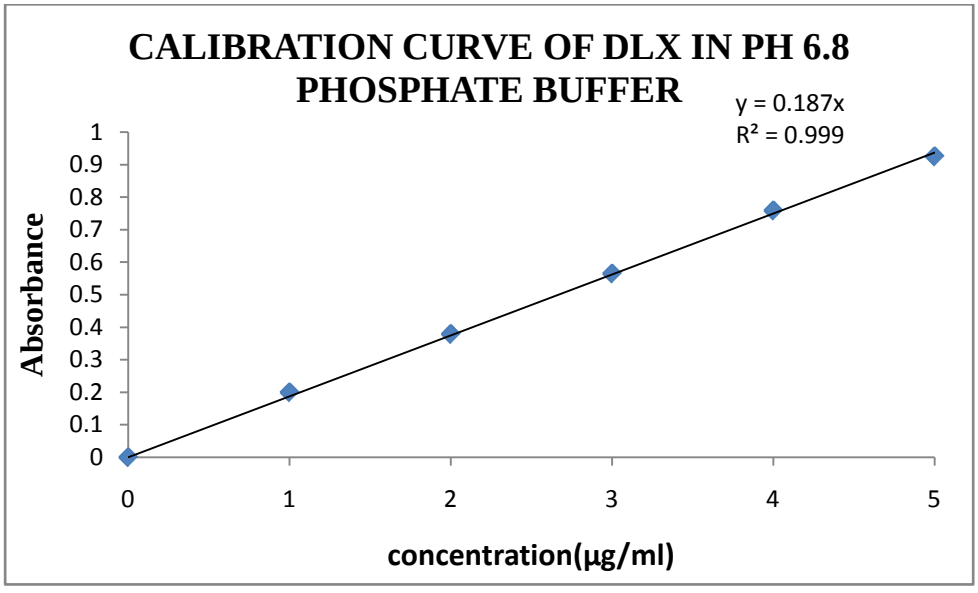


Fig 10: Calibration Curve

FORMULATION DEVELOPMENT

Formulation development of Duloxetine Hcl delayed release capsule containing mini tablets Formulation of dulolxetineHcl mini tablets includes following steps

Stage 1: Direct compression of Mini tablets

It involves direct compression of Duloxetine Hcl lubricated blend

Stage 2: Barrier coating of mini tablets

It involves 20% barrier coating on the core mini tablet.

Stage3: Enteric coating of barrier coated mini tablets

The process of enteric coating includes spraying of enteric polymer on the barrier coated of mini tablets.

The three enteric coating polymers used are

1. Acryleze MP
2. Hydroxy propyl methyl cellulose acetate succinate MF
3. Sureteric and NS Enteric(25:75)

STAGE 1: DIRECT COMPRESSION OF MINI TABLETS

Table No: 12 Formula For Direct Compression Of Mini Tablets

S.No	Ingredients	For One Mini Tablet(mg)	For One Capsule(mg)
1	Duloxetine Hcl	16.83	67.3
2	Minrocrystalline cellulose PH102	18.9	75.6
3	Lactose Monohydrate	18.9	75.6
4	Klucel	3.0	12
5	Sodium starch glycolate	1.8	7.2
6	Magnesium Stearate	0.6	2.4

16.83 mg of Duloxetine Hcl is equal to 15mg of Duloxetine

67.30 mg of Duloxetine Hcl is equal to 60mg of Duloxetine

Procedure:

1) All the ingredients were accurately weighed and passed through ASTM#40 mesh except magenesium stearate.
2) The above material was prelubricatedin a polybag for 20minutes
3) Then Magnesium stearate was passed through ASTM #60 mesh
4) Then Magnesium stearate was added and the above blend was lubricated for 5 minutes in a polybag
5) Then it was compressed by using multi tip punch tooling (4.5mm)

Compression parameters:

Table No: 13 Compression Parameters For Direct Compression Of Mini Tablets

Weight of the tablets	240 mg ± 7.5 %
Hardness	4.0 – 4.7 kP
Disintegration time	2- 2.5 minutes
Thickness	3.3 – 3.4 mm

STAGE II: BARRIER COATING

Barrier coating was done on the core mini tablets to avoid the interaction of drug with the enteric polymer. Due to acidic nature of enteric coating it will react with the drug and cause incompatibility therefore barrier coating was applied.

Criteria for the selection of barrier coating material:

1) Excipient with low free acid content
2) Non hygroscopic material

Table No: 14 Formula For Optimisation Of Barrier Coating.

S.No	**Ingredients**	**mg/unit**			
		F1	F2	F3	F4
1	Drug mini tablets	240	240	240	240
2	Hydroxypropylmeth-ylcellulose 3cps	19.2	19.2	19.2	19.2
3	Talc	28.8	28.8	28.8	28.8
4.	Purified water	q.s	q.s	q.s	q.s
5.	Tablet Wt. per unit capsule	288	288	288	288

30 % overages.solid content 15 % w/w

Procedure

Preparation of barrier coating suspension

Accurate quantity of HPMC 3cps was weighed and then added to purified water under vortex and was stirred to dissolve it and get a clear solution.

Weighed quantity of talc was added and stirred to get a homogeneous suspension. Then the suspension was passed through ASTM#40 mesh

Coating of barrier suspension:

The tablets were taken and prewarmed for ten mins and then barrier coating solution was sprayed and coating was done with below mentioned process parameters

Table No: 15 Process Parameters For Barrier Coating

Atomisation pressure	1.1 bar
Inlet Temperature	42ºC
Pan Rpm	22-25 RPM
Bed Temperature	36
Spray Rate	4-8gm/min
Process Time	4 hrs

STAGE 3: ENTERIC COATING

Duloxetine hcl degrades in the acidic environment so it is important to by pass the acidic pH of the stomach. Protection of the drug from acidic environment and promoting the drug release in the intestinal pH enteric coating of the drug was attempted.

Strategy:

Different build ups of enteric coating with Acryleze MP, HPMCAS MF, and sureteric and NS enteric was done and each batch was evaluated based on its gastric resistance and drug release in pH 6.8 phosphate buffer.

Optimization of Enteric coating build up with Acryleze MP

Method:

Enteric coating suspension with varying quantity of AcrylezeMP polymer , Enteric coating suspension was prepared and coated on barrier coated mini tablets the formula for enteric coating with acrylase MP is given below.

Table No: 16 Formula For Optimization Of Enteric Coating Build Up With Acryleze Mp

S.No	Ingredients	F1-(20%) (mg)	F2-(25%) (mg)	F3- (30%) (mg)
1	Barrier coated mini tablets	288	288	288
2	Acryleze MP	53.856	66.96	80.352
3	PVP K30	3.73824	4.608	5.616
4	Purified water	345.6	360	374.4
	Tab wt per capsule	336	350	364

*20 % overages 15 % w/wsolid content

Procedure:

Preparation of enteric coating suspension:

1) The purified water was divided in to two equal parts.

2) Povidone K30 wasaccurately weighed and addedto purified water under vortex and was stirred to get a clear solution.

3) Acryleze MP wasaccurately weighed and added to the above soltution and was stirred for 45 minutes to get a uniform dispersion.

4) Both were mixed and stirred to get a uniform dispersion.

5) The above enteric coating suspension was sprayed on barrier coated mini tablets using conventional coating pan.

Process parameters :

Table No: 17 Process Parameter For Entering Coating With Acryleze Mp

Inlet Temperature	36-38ºC
Bed Temperature	32 ºC
RPM	20-25 minutes
Atomization pressure	1.1 bar
Process time	4hrs

OPTIMIZATION OF ENTERIC COATING BUILD UP WITH HYDROXY PROPYL METHYLCELLULOSE ACETATE SUCCINATE MF

Strategy:

To take batches with different build up of enteric coating with Hydroxy propyl methyl cellulose acetate succinate MF and to finalize the build up on the basis of acid resistance and dissolution (Acid followed by pH 6.8 Phosphate buffer).

Method:

Enteric coating suspension with varying quantity of HPMC AS MF polymer, Enteric coating suspension were prepared and coated on barrier coated mini tablets the formula for enteric coating with HPMC AS MF is given below.

Table No 18: Formula For Optimization Of Enteric Coating Build Up With Hydroxy Propyl Methylcellulose Acetate Succinate Mf

S.No	Ingredients	F1-(20%) (mg)	F2-(25%) (mg)	F3-(30%) (mg)
1	Barrier coated mini tablets	288	288	288
2	HPMC AS MF	41.15	51.44	61.72
3	TEC 20%	8.22	10.28	12.33
4	Talc 30%	12.34	15.43	18.51
5	Purified water	q.s	q.s	q.s
	Tablet wt/unit capsule	336	350	364

Procedure:

Preparation of enteric coating suspension:

1) Tri Ethyl Citrate was added to purified water and stirred for 10 minutes

2) HPMC AS MF was added to the above solution and talc was gradually added and stirred for 20minutes

3) Thenthe above suspension was passed through ASTM#40

4) 28%w/v of NaoH solution was prepared and neutralization was started.

5) The above enteric coating suspension was sprayed on barrier coated mini tablets using conventional coatingpan

Process parameters:

Table No: 19 Process Parameter For Enteric Coating With Hpmc As Mf

Inlet Temperature	40-45ºC
Bed Temperature	32 ºC
RPM	20-25 minutes
Atomization pressure	1.1 bar
Process time	5hrs

OPTIMIZATIONS OF ENTERIC COATING BUILD UP WITH SURETERIC AND NS ENTERIC:

Strategy:

To take batches with different build up of enteric coating with Sureteric And NS Enteric and to finalise the build up on the basis of acid resistance and dissolution (Acid followed by pH 6.8 Phosphate buffer).

Method:

Enteric coating suspension with varying quantity of Sureteric And NS Enteric were prepared and enteric coating suspension was coated on barrier coated mini tablets the formula for enteric coating with Sureteric And NS Enteric is given below.

Table No: 20 Formula For Optimizations Of Enteric Coating Build Up With Sureteric And Ns Enteric

S.No	Ingredients	F1-(2%) (mg)	F2-(4%) (mg)	F3-(6%) (mg)
1	Barrier coated mini tablets	288	288	288
2	NS Enteric	4.32	8.64	12.96
3	Sureteric	1.44	2.88	4.32
4	Purified water	q.s	q.s	q.s
	Tablet wt/unit capsule	285.6	291.2	296.8

Procedure:

Accurately weighed quantity of NS enteric was added to the required quantity of purified water and stirred for 20 minutes

Accurately weighed quantity of Surelasedispersion(containing 30% solids) was added and stirred for 20 minutes The above preparations was mixed and stirred for 30 mins to get a uniform suspension

Then the above suspension was passed through ASTM#40 mesh

Process parameters:

Table No: 21 Process parameter for entering coating with Sureteric and NS Enteric

Inlet Temperature	40-45ºC
Bed Temperature	32 ºC
RPM	20-25 minutes
Atomization pressure	1.1 bar
Process time	5hrs

RESULTS & DISCUSSION

Preformulation studies

Table No: 22 Characterization of API

S.No	Characteristics	Results
1	Description	White to off white powder
2	Solubility	Soluble in ph 6.8 phosphate buffer,very soluble in methanol,sparingly soluble in water
3	Bulk Density	0.220gm/cc
4	Tapped Density	0.460 gm/cc
5	Carrs index	52.17
6	Haushner ratio	1.02
7	Angle of reporse	44.6

From the above results it has been concluded that API has poor flow property

Evaluation of mini tablets

Table no 23: Evaluation of Mini Tablets

S.NO	WEIGHT VARIATION (mg)	HARDNESS (Kp)	THICKNESS (mm)	DISINTEGRATION TIME (mins)
1	**60**	**4.1**	**3.30**	**2 min 10 sec**
2	**59**	**4.2**	**3.33**	**2 min 18 sec**
3	**59**	**4.0**	**3.40**	**2 min 13 sec**
4	**61**	**4.5**	**3.36**	**2 min 21 sec**
5	**60**	**4.7**	**3.32**	**2 min 26 sec**

6	**59**	**4.4**	**3.35**	**2 min 28 sec**
7	**61**	**4.2**	**3.37**	**2 min 27 sec**
8	**60**	**4.1**	**3.30**	**2 min 19 sec**
9	**60**	**4.7**	**3.31**	**2 min 14 sec**
10	**60**	**4.4**	**3.36**	**2 min 21 sec**
11	**61**	**4.6**	**3.38**	**2 min 26 sec**
12	**61**	**4.2**	**3.37**	**2 min 27 sec**
13	**60**	**4.4**	**3.31**	**2 min 29 sec**
14	**58**	**4.3**	**3.32**	**2 min 20 sec**
15	**60**	**4.1**	**3.35**	**2 min 21 sec**
16	**61**	**4.5**	**3.31**	**2 min 18 sec**
17	**60**	**4.1**	**3.36**	**2 min 26 sec**
18	**61**	**4.2**	**3.36**	**2 min 27 sec**
19	**62**	**4.5**	**3.39**	**2 min 24 sec**
20	**60**	**4.6**	**3.38**	**2 min 31 sec**

Friability:

5 sets of tablets were taken and friability tests were conducted in rochefriabilator and the results are given below

Table No: 24 Friability Values of Mini Tablets

S.NO	FRIABILITY (%)
SET 1	0.35
SET 2	0.56
SET 3	0.45
SET 4	0.60
SET 5	0.40

Assay:

The mini tablets were assayed for drug content after under going dissolution at USP 1 (basket) at 100 rpm, 1000ml, 0.1N Hcl for 2hrs and the values are given

Table No: 25 Assay Values of Mini Tablets

S.No	Formulation	Assay value
1	F_1	99.7±0.1

BARRIER COATING:

Barrier coating is done to prevent the interaction between the drug and enteric coating material.The 20% of barrier coating was optimized through stability studies.

RESULTS FOR OPTIMISATIONS OF ENTERIC COATING BUILD UP WITH ACRYLEZE MP:

Tooptimize the build up of enteric coating with Acryleze MP different trials were taken & it is evaluated on the basis of acid release & dissolution. The results are presented below.

Dissolution (0.1N HCL followed by pH 6.8 phosphate buffer)

USP1 (Basket),100RPM ,1000ml 0.1N HCL for 2 hours followed by 1000ml pH 6.8 phosphate buffer and sampling is done at time intervals of 15,30,45,60,90, 120 minutes.

Table No: 26 Effect of enteric coating build up on dissolution of batch made with Acryleze MP.

TIME	F1 (20%)	F2 (25%)	F3 (30%)
ACID RELEASE			
120	0	0	0
pH 6.8 PHOSPHATE BUFFER			
135	54	55	45
150	74	75	52
165	79	82	65
180	80	92	72
210	84	96	78
240	86	98	83

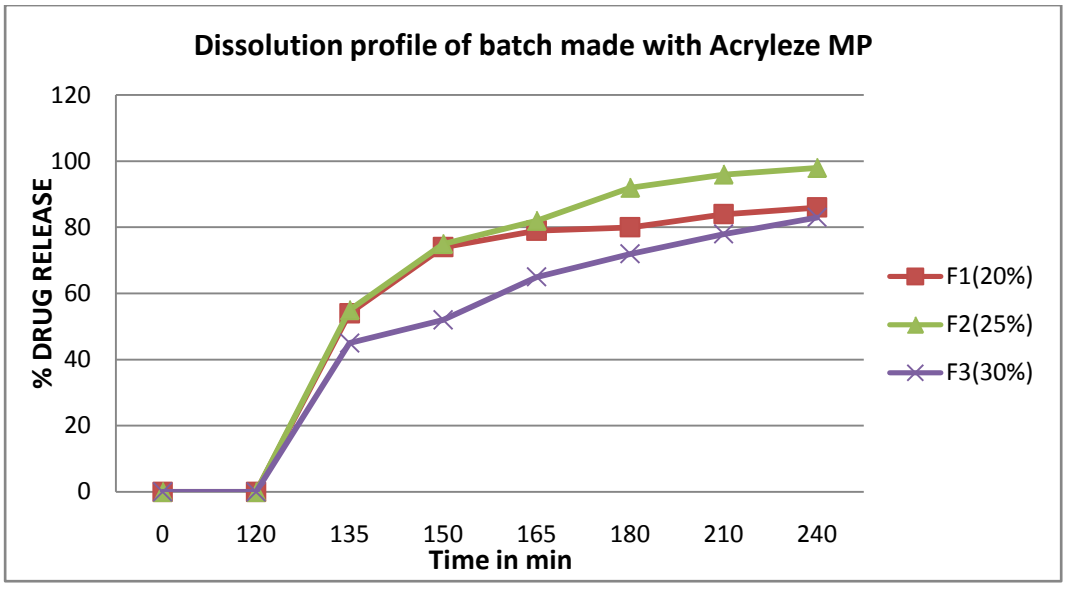


Figure 11: Effect of enteric coating build up with Acryleze MP on dissolution

DISCUSSION:

From the above results is clearly evident that the batch made up with 25% enteric coating of Acryleze MP shows higher similarity factor with the innovator product dissolution and it was found to be better than other batches dissolution. The batch with 20% build up shows no acid release but the dissolution got hampered. But batch with 25% showed better dissolution profiling then 20% and 30%. All the 3 batches have passed in gastric resistance. The process with Acryleze MP aqueous suspension was found to be efficient and it is economical and safe.

RESULTS FOR OPTIMISATIONS OF ENTERIC COATING BUILD UP WITH HPMC AS MF:

Tooptimize the build up of enteric coating with HPMC AS MF different trials were taken & it is evaluated on the basis of acid release & dissolution. The results are presented below.

Dissolution (0.1N HCL followed by pH 6.8 phosphate buffer)

USP1 (Basket),100RPM ,1000ml 0.1N HCL for 2 hours followed by 1000ml pH 6.8 phosphate buffer and sampling is done at time intervals of 15,30,45,60,90, 120 minutes

Table No: 27Effect of enteric coating build up on dissolution of batch made with HPMC AS MF.

TIME	F1 (20%)	F2 (25%)	F3 (30%)
ACID RELEASE			
120	0	0	0
pH 6.8 PHOSPHATE BUFFER			
135	38	30	27
150	70	62	58
165	86	76	71
180	94	83	78
210	97	93	82
240	99	96	89

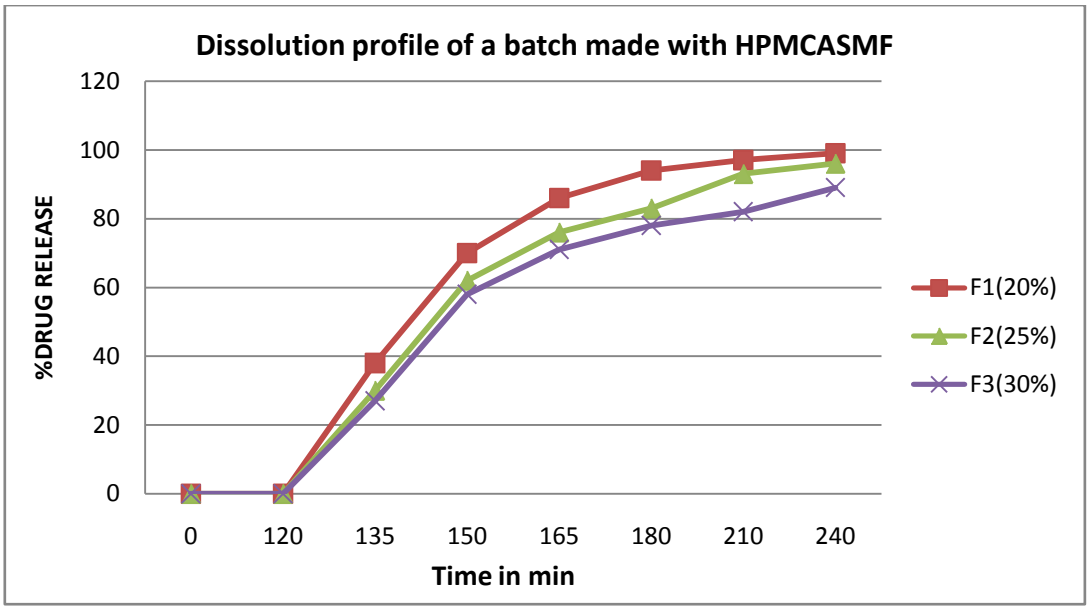


Figure: 12 Effect of enteric coating build up on dissolution of batch made with HPMC AS MF**.**

DISCUSSION

From the above results is clearly evident that the batch made up with 20% enteric coating of HPMC AS MF shows highest similarity factor with the innovator product and it was found to be better than other batches dissolution. The batch with 25% build up shows no acid release but the dissolution got hampered. But batch with 20% showed better dissolution profiling then 25% and 30%. All the 3 batches have passed in gastric resistance. The process with HPMC AS MF Non aqueous suspension was found to be critical due to fine generation and consumption of huge quantity of solvent.

RESULTS FOR OPTIMISATIONS OF ENTERIC COATING BUILD UP WITH SURETERIC AND NS ENTERIC:

Tooptimize the build up of enteric coating with SURETERIC AND NS ENTERIC different trials were taken & it is evaluated on the basis of acid release & dissolution. The results are presented below.

Dissolution (0.1N HCL followed by pH 6.8 phosphate buffer)

USP1 (Basket),100RPM ,1000ml 0.1N HCL for 2 hours followed by 1000ml pH 6.8 phosphate buffer and sampling is done at time intervals of 15,30,45,60,90, 120 minutes

Table No: 28 Effect of enteric coating build up on dissolution of batch made with SURETERIC AND NS ENTERIC

TIME	F1 (2%)	F2 (4%)	F3 (6%)
ACID RELEASE			
120	0	0	0
pH 6.8 PHOSPHATE BUFFER			
135	28	24	21
150	36	32	30
165	54	46	42
180	74	63	59
210	79	69	61
240	88	79	72

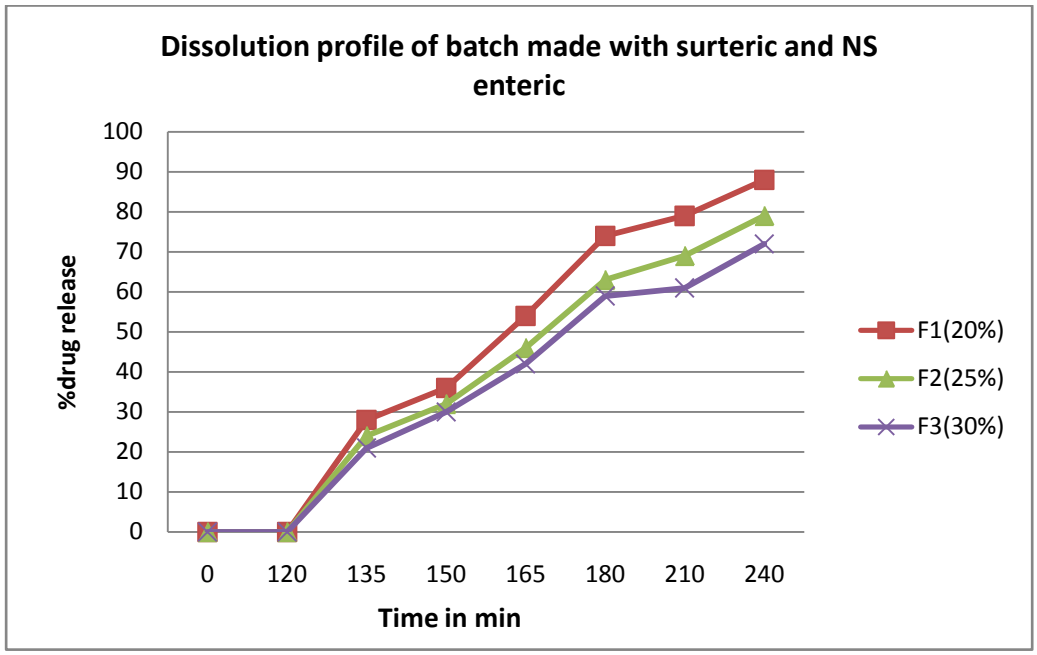


Figure:13 Effect of enteric coating build up on dissolution of batch made with SURETERIC AND NS ENTERIC

DISCUSSION:

The batch made up with 2% enteric coating of sureteric and NS enteric shows good dissolution profile than other batches dissolution when compared to innovator product.The batch with 2% build up shows no acid release but the dissolution got hampered. But batch with 4% and 6% showed low dissolution profile .All the 3 batches have passed in gastric resistance. The process with SURETERIC AND NS ENTERIC aqueous suspension was found to be efficient and it is economical and safe.

PHARMACEUTICAL EQUIVALENCE STUDIES:

REFERENCE AND IN HOUSE PRODUCT CHARACTERIZATION:

Table No: 29 Reference and in House Product Characterization:

PARAMETERS	REFERENCE PRODUCT	IN HOUSE PRODUCT
Description	Opaque green body and opaque blue cap, and is imprinted with “60 mg” on the body and “LILLY 3237” on the cap	Blue cap/Green body, Size 1, hard gelatin capsule, imprinted with “OHC” on cap with white ink and “60mg” on body with black ink, filled with white to off white pellets
Fill weight (mg)	332.5	343.45
Assay	101.3 %	99.80%
Water by KF	2.0 %	2.4%

Acid stage release of Cymbalta® delayed release capsules 60 mg

The acid stage release of Cymbalta® delayed release capsules 60 mg is presented below

Medium : 0.1N Hcl

Dissolution type : USP I (Basket)

RPM : 100

Media Volume : 1000ml

Table: 30 Acid Stage Release Of Reference Product

	Cymbalta® delayed release capsules 60mg			**Average % Drug released**
	% Drug released			
Time	Unit 1	Unit 2	Unit 3	
2 hours	0.9	2	1.8	1.57

Dissolution profile in 0.1N HCl for 2 hours followed by pH 6.8 Phosphate buffer

Medium : 0.1N HCl for 2 hours followed by pH 6.8 Phosphate buffer

Dissolution type : USP I (Basket)

RPM : 100

Media Volume : 1000ml

Table No: 31Dissolution of Reference Product at Ph 6.8 Phosphate Buffer

Time (min.)	Cymbalta® delayed release capsules 60mg			Average % drug dissolved
	Cumulative % drug dissolved			
	Unit 1	Unit 2	Unit 3	
15	36.3	40.4	38.4	38.37
30	66.5	70.4	68.3	68.4
45	78.5	82.6	81.6	80.9
60	84.3	88.5	86.5	86.44
90	90.8	93.7	92.2	92.24

Table no:32 Comparative desolution profile of innovator produst with different buid up of enteric coated polymers used.

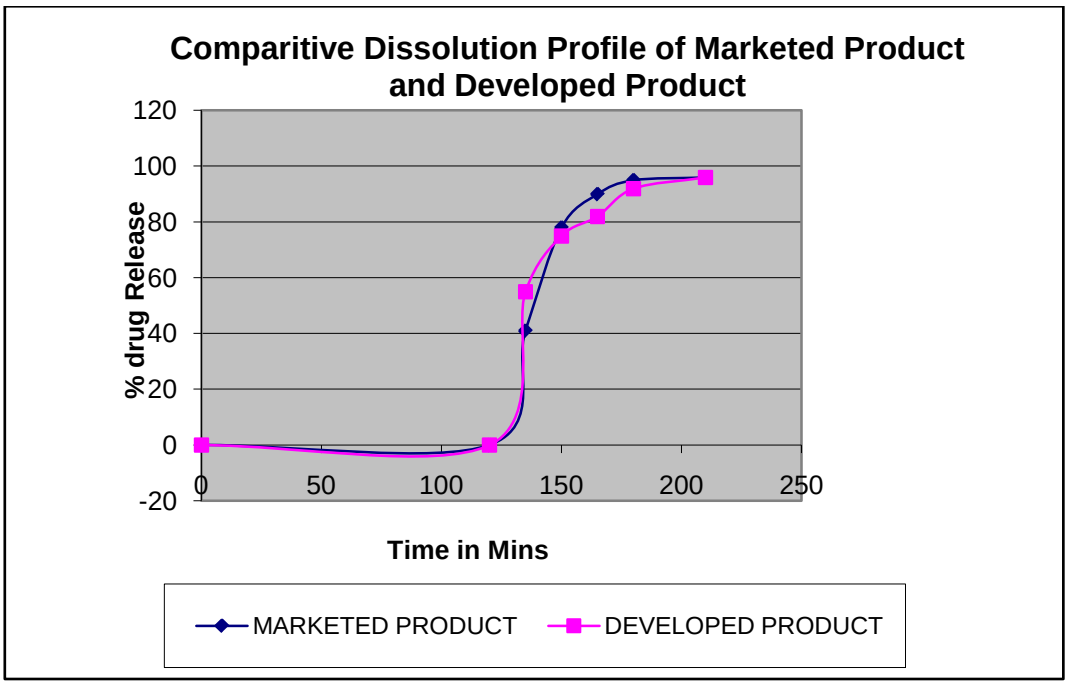
S.NO	TIME MINS	INNOVATOR	ACRYLEZE MP			INNOVATOR	HPMC AS MF			INNOVATOR	NS ENTERIC AND SURETERIC		
			F1 (20%)	F2 (25%)	F3 (30%)		F4 (20%)	F5 (25%)	F6 (30%)		F7 (2%)	F8 (4%)	F9 (6%)
1	120	0	0	0	0	0	0	0	0	0	0	0	0
2	135	41	54	55	45	41	38	30	27	41	28	24	21
3	150	78	74	75	52	78	70	62	58	78	36	32	30
4	165	90	79	82	65	90	86	76	71	90	54	46	42
5	190	95	80	92	72	95	94	83	78	95	74	63	59
6	210	96	84	96	78	96	97	93	82	96	79	69	61
7	240	98	86	98	83	98	99	96	89	98	88	79	72

Discussion:

On the basis of results obtained for acid release and dissolution profile of the 3 enteric coating polymers made with different build ups Acryleze MP 25% was found to have highest similarity with the innovator product and as it is a aqueous base and economical and safe compared to other formulations Acryleze MP 25% was selected as optimized formulation

Table no.33 Comparative Dissolution Profile of Marketed Product and Developed Product

TIME	MARKETED PRODUCT	DEVELOPED PRODUCT
0	0	0
120	0	0
135	41	55
150	78	75
165	90	82
180	95	92
210	96	96
240	98	98



Comparative Dissolution Profile of Marketed Product and Developed Product

DISCUSSION

The comparative study of developed product with the marketed product shows that both are pharmaceutically equivalent

CONCLUSION

Duloxetine hydrochloride is an acid labile drug which degrades at the acidic pH of the stomach so duloxetine hydrochloride multi particulate has been designed as gastroresistant mini tablets. The preformulation studies of Duloxetine hydrochloride including the drug excipient compatibility has been conducted and the formulation is developed in such a way to release the drug in small intestine and keep the formulation stable for a long time.

Multiparticulate formulation has enormous advantages over all other oral dosage forms, especially in modified release formulation thus Duloxetine is made as multiparticulate drug delivery system. And the formulation is made in fluidised bed processor (wurster process), using bottom spray.

The enteric system of duloxetine was evaluated with 3 polymers with various percentage build ups and evaluated for acid resistance and dissolution profile The initial result indicates, the product is having good acid resistant, when it exposed to acidic environment, and having good dissolution profile in pH 6.8 phosphate buffer, and comparable to the marketed formulation.

Stability study is initiated.

BIBLIOGARPHY

1. NS Dey, S Majumdar and MEB Rao. *Multiparticulate Drug Delivery Systems for Controlled Release,* Tropical Journal of Pharmaceutical Research, September 2008. p.1067-1075.
2. Erik Greb. *The Hour of the Particle, Pharmaceutical Technology*, Jul 2, 2010, Vol 34, Issue7. p.38-42.
3. Tang E. S.K., Chan L.W, Heng P.W.S, *Coating of Multiparticulates for Sustained Release, Amer J Drug Delivery 2005: 3(1): 17-28).*
4. *Intestinal protective drug absorption system, Elan Corporation, U.S.Patent 75111480, Nov 4,1997.)*
5. *Spheroidal oral drug absorption system, Elan Corporation, U.S.Patent 73700314, Nov21,1989.)*
6. Programmable oral drug absorption system, Elan corporation, U.S. Patet 75283262, june27,2000.
7. *http://www.eurand.com*
8. *Diffucaps in multiparticulate drug delivery, Eurand S.P.A. Corporation, U.S. Patent 72329344,Feb29, 1972)*
9. *Fegely K. Articles base-Mini-Tablets Offer Mighty Advantages to the Pharmaceutical Industry. [Online].; 2009 [cited 2010 10 26]. Available from: HYPERLINK "http://www.articlesbase.com/medicine-articles/minitablets-offer-mighty-advantages-to-the-pharmaceutical-industry-1056960.html" http://www.articlesbase.com/medicine-articles/minitablets-offer-mighty-advantages-to-the-pharmaceutical-industry-1056960.html*

10. *Desset-Brethes S. Patient Centricity: Minitabets (granules), an innovative dosage form for children. In EuPFI Conference-Formulating Better Medicines for Children; 2009; London. p. 1-6.*
11. *Lopes CM, Lobo JMS, Pinto JF, Costa P. Compressed mini-tablets as a biphasic delivery system. International Journal of Pharmaceutics. 2006 October; 323(1-2): 93-100.*
12. *Ishida M, Abe K, Hashizume M, Kawamura M. A novel approach to sustained pseudoephedrine release: Differentially coated mini-tablets in HPMC capsules. International Journal of Pharmaceutics. 2008 July; 359(1-2): 46-52.*
13. *Brabander DC, Vervaet C, Fiermans L, Remon JP. Matrix mini-tablets based on starch/microcrystalline wax mixtures. International Journal of Pharmaceutics. 2000 April; 199(2): 195-203.*
14. *trommsdorff web site.[Online]. [cited 2010 October 27]. Available from: HYPERLINK "http://www.trommsdorff.de/fileadmin/trommsdorff/redaktion/downloads/Broschuere_LH_engl.pdf" http://www.trommsdorff.de/fileadmin/trommsdorff/redaktion/downloads/Broschuere_LH_engl.pdf .*
15. *carol holquist , and walter fava, A look at delayed Vs Extended release Rxs. Drug topics,2007.p.56*
16. *howars C Ansel. :yod, V Allen , Nicholas, G Popvith. Ansels Pharmaceutical dosage forms and drug deliver systems. 8th ed Baltimore; Lippincott willams & wilkins 2005, pg68*
17. *Peck ge Baley G.J Mc curdy V.E Banker, G.S Tablet Formulation Design. Tablets Arcel Decker Newyork 1989, 75-130*
18. *http://en.wikipedia.org*
19. S.Bozdag, S.Çalız, M.Sumnu. *Formulation and In Vitro Evaluation of Enteric Coated Omeprazole Formulations.* S. T. P.Pharma Sciences, 1999, p. 321-327.

20. Laila Fatima Ali Asghar and Sajeev Chandran. *Multiparticulate Formulation Approach to Colon Specific Drug Delivery,* Current Perspectives. J Pharm Pharmaceut Sci. 2006, p. 327-338.
21. *Brahma N. Singh . Modified Release Solid Formulations For Colonic Delivery Recent Patent on Drug Delivery And Formulations 2007 p53-63.*
22. *Paresh Prajapathi A. etal 2010 Evaluation of controlled release ophthalmic mini tablets prepared by Direct compression Int , J . Pharm 2-30*
23. *Dominico D Berardis etal 2007.,*
24. *Smith T, Nicholson RA. Review of Duloxetine in the Management of Diabetic Peripheral Neuropathic Pain.Vascular Health and Risk Management. 2007; 3(6): 833-844.*
25. *Hunziker ME, Suehs BT, Bettinger TL, Crismon LM. Duloxetine Hydrochloride: A New Dual-Acting Medication for the Treatment of Major Depressive Disorder. Clinical Therapeutics. 2005 August; 27(8): 1126-1143.*
26. *Islam MR, Ahmed I, Rahman HM. Delayed Release Pharmaceutical Pellets having Duloxetine Hydrochloride Containing Core and Acid Resistant Acrylic Polymer based Outer Layer Coat. Bangladesh Pharmaceutical Journal. 2010 January; 13(1): 9-13.*
27. Nele Poelvoorde. *Development of a Multi-Particulate Formulation of Viable Bacteria for Oral and Vaginal Delivery*. 2009, (http://hdl.handle.net/1854/LU-610271).
28. V.M. Castano M. Gonzalez, Rieumont, D Dupeyron, I. Perdomo, E. Fernandez, L. Abdon. *Nanoencapsulation of Acetyl Salicylic Acid within Enteric Polymer Nanoparticles* Rev.Adv.Master Sci, Vol 17, 2008, p.71-75.

29. Fude Cui, Yongsheng Wang, Jiamiao Wang, Lili Feng and Keji Ning. *Preparation of an Enteric Soluble Solid-State Emulsion Using Oily Drugs.* International Journal of Pharmaceutics, 2007, p.152–156.
30. Pao Chu Wu, Yaw-Bin Huang, Chia Hung Sung, Ren Jiunn Wang and Yi Hung Tsai. *The Effect of Eudragit and Enteric Polymer Composite on the Release of Nicardipine*. Journal of Food and Drug Analysis, Vol. 14. 2006, p. 334-339.
31. Su-Yun Lyu1, Young-Ju Kwon, Hye-Jin Joo, and Won-Bong Park. *Preparation of Alginate/Chitosan Microcapsules and Enteric Coated Granules of Mistletoe Lectin* Arch. Pharm Res Vol 27, 2004. P.118-126.
32. *Shin Etsu Chemical (2006)*
33. Patrick J. Jansen , Peter L. Oren, Craig A. Kemp, Steven R. Maple, Steven W. Baertschi. *Characterization of Impurities Formed by Interaction of Duloxetine HCl with Enteric Polymers Hydroxypropyl Methylcellulose Acetate Succinate and Hydroxypropyl Methyl Cellulose Phthalate*, Journal of Pharmaceutical Sciences, 1998, Vol 87. p.81-85.
34. Gang Cheng, Feng An, Mei-Juan Zou, Jin Sun, Yun-Xia He. *Time and pH Dependent Colon-Specific Drug Delivery for Orally Administered Diclofenac Sodium and 5-Aminosalicylic acid.* World J Gastroenterol 2004, p.1769-1774.
35. Norihito Shimono, Toshihito Takatori, Masumi Ueda, Masaaki Mori, and Yasuhiko Nakamura. *Multiparticulate Chitosan-Dispersed System for Drug Delivery*. Chem.Pharm, Vol 56, 2003. p. 620-624.
36. *Sureteric colorcon.com*

37. *http://www.freepatentsonline.com*

38. *http://www.medicinenet.com/depression/focus.htm*

39. *http://www.nevdgp.org.au/info/topics/depression_intro.htm*

40. *http://www.rxlist.com*

41. *http://www.dailymed.com*

42. http://www.who.int/mental_health/management/depression/depressioninph/en/

43. *Handbook of pharmaceutical Excipients 5th Edition,pg 1043-1067*